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URETEROCUTANEOUS ANASTOMOSIS WITHOUT THE USE OF CATHETERS

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•Cutaneous ureterostomies were made necessary in 22 patients by vesical carcinoma and other diseases of the lower urinary tract. The ureterostomy incision for the technique here described was usually 5 cm. medial and superior to the anterior superior iliac spine. The operation was done in two stages. Ipsilateral transplantation was done as the first stage; contralateral transplantation plus the other required surgery on the bladder or kidney was done as the second stage. It was essential to observe certain precautions as to the handling of the ureter and the site of the stoma; a temporary indwelling catheter was used to prevent leakage of urine and wetting of the surrounding tissues. Analysis of nine cases of fair or poor results showed that the primary cause of trouble was necrosis and retraction at the end of the ureter. Experience with 13 cases with satisfactory results showed that the catheter can be removed after 12 to 14 days and that normal renal function can be maintained over a period of years thereafter.

Ureterocutaneous anastomosis has never been a popular method of diverting the urine stream. Although ureterosigmoidostomy has been the method of choice, it is well recognized that disturbances of electrolyte balance and pyelonephritis are troublesome and sometimes fatal complications of this procedure. The use of the so-called substitute bladder constructed from part of the intestinal tract for the collection of urine has not been completely satisfactory.

The unquestioned advantages of cutaneous ureterostomy are the lower morbidity and mortality rates and the absence of electrolyte alterations. The disadvantages of this procedure are the possible development of ureteral stricture with secondary hydronephrosis, the need for indwelling ureteral catheters with the associated development of pyelonephritis, and the inconvenience and difficulty of caring for the apparatus used for collection of the urine.

Eleven years ago a surgical technique for ureterocutaneous anastomosis was presented by one of us [1] that was designed to eliminate ureteral strictures and the need for indwelling ureteral catheters. This permits the use of a simple apparatus for urine collection. The purpose of this report is to reevaluate the merits of this technique and to present the end-results in a group of 22 patients observed during the past 18 years.

Operative Technique

The usual ureterostomy incision is made 5 cm. medial and superior to the anterior superior iliac spine (fig. 1). The incision is extended superiorly as required to mobilize the ureter and to secure a straight line of drainage from the kidney. The ureter is incised at or below the iliac arterial bifurcation and brought to the skin without tension. One small Penrose drain is used and brought out at the upper end of the incision. Closure of the muscles is in layers by interrupted sutures of 0 chromic absorbable surgical sutures.

Skin flaps are made at the site of anastomosis by two parallel incisions 2.5 cm. long and 3.0 cm. apart on either side and perpendicular to the original incision (fig. 1). Each skin flap is folded under by two mattress sutures of silk (fig. 2). The ureter is incised longitudinally at its distal end for 1.5 cm. A subdermal tunnel is made in the top of each infolded skin flap, and the incised half of the ureter is drawn into the appropriate subdermal channel and fixed in place with 00000 atraumatic silk suture (fig. 2). The infolded skin flaps are then sutured together across the incision to relieve any tension on the split ends of the ureter (fig. 3). A soft rubber ureteral catheter is left indwelling for 12 to 14 days. Sutures are removed on the 10th postoperative day.

The procedure is usually performed in two stages, transplantation performed at the first operation and the opposite transplantation and cystectomy or nephroureterocystectomy performed as the second stage.

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Read before the Section on Urology at the 105th Annual Meeting of the American Medical Association, Chicago, June 13, 1956.

At operation it is important to locate the proper site of anastomosis, with the site adapted to the abdominal topography of the patient; to avoid ureteral angulation and tension; to form skin flaps of proper size and adequately infolded; and to tunnel a sufficient length for the insertion of the split ends of the ureter.

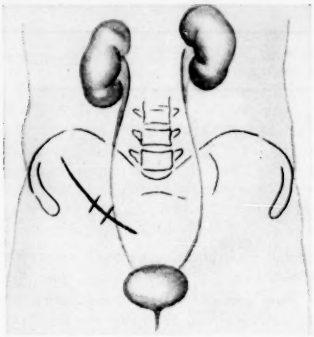

Fig. 1.—Semidiagrammatic drawing showing location of skin incision in relation to the ureter.

The postoperative care of the anastomosis is possibly the most important factor in the success of the operation. The prevention of leakage of urine around the temporary indwelling ureteral catheter and the wetting of the anastomotic site are essential, with constant attention required to prevent obstruction or displacement of the catheter. Inflammation and edema must be prevented to avoid sloughing or avulsion of the embedded ends of the ureter due to tension. Abdominal distention must be avoided because of the resulting tension placed on the ends of the ureter.

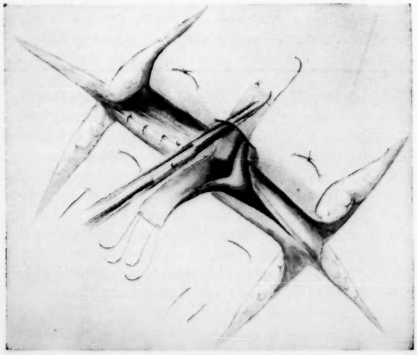

Fig. 2.—Drawing showing first stage in technique of ureterocutaneous anastomosis, the formation of the skin flaps and the subdermal tunneling of the split ends of the ureter.

The apparatus usually used for the collection of urine has been the Singer or the Whitmore cup with an attached rubber or plastic bag. These cups are inexpensive, easy to apply, and easily cleaned.

Results of Ureterostomy in Twenty-two Patients

Sixteen of the 22 patients were treated because of transitional cell carcinoma of the bladder (tables 1 and 2). Ten of these patients died of carcinoma in two months to four years, with an average postoperative life of 13.3 months; in six other patients cystectomy was not performed because of extension of the inoperable carcinoma of the bladder.

The ureterocutaneous anastomoses were satisfactory in 8 of the 10 patients who died of neoplasm. In two cases in which autopsy was performed five months and four years, respectively, after operation there were normal kidneys and ureters with good anastomoses; nephrectomy had been performed in each patient six and nine years previously. Of the two patients with unsatisfactory results, an indwelling ureteral catheter was required in one because of massive metastases producing obstruction of the ureter and requiring colostomy because of obstruction of the descending colon; the other patient died in uremia due to ureteral stricture that was secondary to sloughing and retraction of the split ends of the ureter.

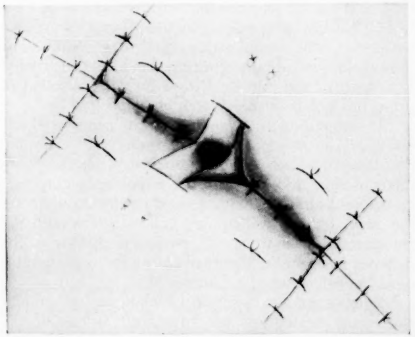

Fig. 3.—Drawing showing second stage in technique of ureterocutaneous anastomosis, the completed anastomosis. Note the sutures approximating the infolded skin flaps to prevent tension on the ureteral ends.

At the time of writing, six patients with carcinoma of the bladder are alive 6, 7, 9, 12, 15, and 21 months after operation. The patient who is alive seven months postoperatively had an inoperable bladder lesion. Three of these patients have excellent anastomoses (fig. 4) and normal upper urinary tracts as demonstrated by intravenous urography (fig. 5), with normal urine findings and blood nonprotein nitrogen levels within normal limits. Three have developed hydronephrosis, one without infection and with a normal blood nonprotein nitrogen level, and two with pyuria (with blood nonprotein nitrogen levels of 36 mg. in one and 95 mg. per 100 cc. in the other). These two patients had sloughing and retraction of the ureter, and ureteral catheter drainage has been instituted.

Bilateral ureteral transplantation and cystectomy was performed in one patient with a carcinoma of the urethra. The ureterocutaneous anastomosis on the left was satisfactory, with a normal kidney on urographic examination and uninfected urine. The ends of the

right ureter became necrotic and sloughed because of postoperative leakage of urine and inflammation resulting in ureteral retraction and stricture at the skin level. Reoperation was performed one and one-half years after the first operation.

TABLE 1.—*Procedures Carried Out in Twenty-two Patients in Whom Ureterocutaneous Anastomoses Were Made*

Disease	No. of Patients	Bilateral Transplant and Cystectomy	Bilateral Transplant	Unilateral Transplant	Unilateral Transplant and Nephroureterocystectomy	Unilateral Transplant and Cystectomy	Unilateral Transplant and Nephrectomy
Vesical carcinoma	16	5	3	3*	3	1	1
Carcinoma of urethra	1	1	...	...	...	...	...
Tuberculosis	2	...	...	2*	...	...	...
Elusive ulcer	2	...	2	...	...	...	...
Neurogenic bladder	1	...	1	...	...	...	...

* One patient had a previous opposite nephrectomy.

One patient with vesical tuberculosis and previous opposite nephrectomy has hydronephrosis that is not altered from that existing prior to transplantation. Drainage with an indwelling ureteral catheter is maintained in this patient because of the loss of the split ends of the ureter that was secondary to postoperative leakage and inflammation of the anastomosis during the healing phase. The second patient with renal and vesical tuberculosis died in uremia four months after operation after complete dehiscence of the incision and ureteral retraction.

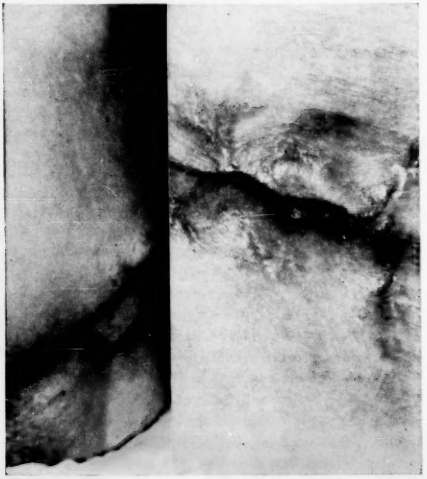

Fig. 4.—*Left*, front view of patient, aged 64, showing location of ureterocutaneous anastomosis on left. *Right*, lateral (close up) view showing anastomosis on right in the same patient with split ureteral ends and infolded skin flaps.

Bilateral ureteral transplantation was performed in two patients with elusive ulcer of the bladder. One is alive 18 years after operation, with normal kidney and normal urine findings. One died one and one-half years after operation of carcinoma of the esophagus. Numerous urinalyses performed before death occurred revealed no infection. At autopsy there was no stricture of the ureters, and the kidneys were normal.

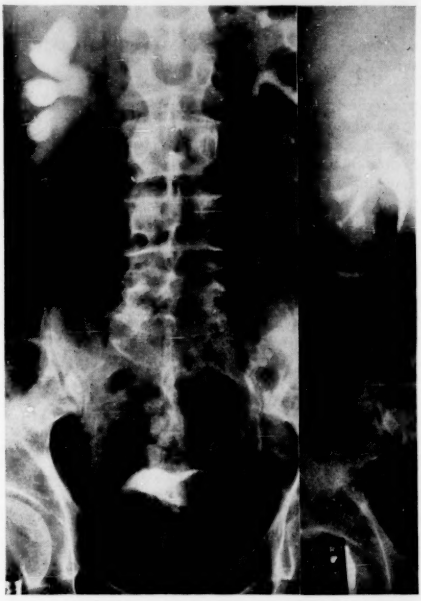

Fig. 5.—*Left*, preoperative excretory urogram of patient in figure 4, showing hydronephrosis on the right and vesical defect due to tumor. *Right*, excretory urogram taken eight months after operation, showing the regression of hydronephrosis on the right.

In the patient with a neurogenic bladder and hydronephrosis on the right that was secondary to congenital meningocele, the anastomoses were entirely satisfactory. She is still living 10 years after operation, with normal intravenous urograms and normal urine.

TABLE 2.—*Results of Ureterocutaneous Anastomoses in Twenty-two Patients*

Disease	No. of Patients	No. of Ureters Transplanted	No. of Ureters Developing Necrosis and/or Stricture
Vesical carcinoma	16	24	5
Carcinoma of urethra	1	2	1
Tuberculosis	2	2	2
Elusive ulcer	2	4	...
Neurogenic bladder	1	2	...
Totals	22	34	8

Comment

A résumé of the 22 cases of cutaneous ureterostomy reveals an achievement of desired results in 13 patients, fair results in 5 patients, and poor results in 4 patients.

Of the 13 patients with good results, 5 are alive with normal renal function, as demonstrated by intravenous urography, urinalysis, and blood nonprotein nitrogen

studies. Seven are dead of vesical carcinoma, and one is dead of an esophageal carcinoma. Prior to death these patients had developed no ureteral strictures, did not require the use of ureteral catheters, and had normal urine findings.

Of the five patients with only fair results, three developed necrosis of the ends of the ureter. Of the three patients, one with an adequate ureterostomy died postoperatively of septicemia, with an opposite pyonephrosis being the infective focus; in one there was unilateral stricture of the ureter with a satisfactory opposite ureterostomy; and in one there was mild hydronephrosis and pyuria. One of the five patients developed a moderate hydronephrosis, without stricture or infection. One patient was classified in this group because of the need of drainage with a ureteral catheter due to obstruction of the ureter secondary to periureteral metastases.

The four patients classified as having poor results include two with tuberculous infection of the urinary tract, one with dehiscence of the entire incision who died from uremia and a second with a ureteral stricture and continuing hydronephrosis necessitating the use of an indwelling ureteral catheter. The third patient, who died in uremia, developed ureteral necrosis, ureteral retraction, and stricture. The fourth patient developed necrosis of the ends of the ureter, stricture, and hydronephrosis (with a nonprotein nitrogen level of 95 mg. per 100 cc.), requiring the use of an indwelling ureteral catheter. Two months after catheter drainage was begun the nonprotein nitrogen level was 60 mg. per 100 cc.

The primary cause of any degree of failure of the procedure in these patients was necrosis of the split ends of the ureter, with sloughing and stricture. This occurred in the immediate postoperative period and was generally associated with contamination of the incision by leakage of urine around the indwelling catheter and with secondary inflammation of the anastomotic site. A second but minor cause of failure in this series was undue ureteral tension, with retraction, ureteral necrosis, and stricture formation in the depths of the skin folds. It is essential to remember that surgical preciseness in constructing the anastomosis and careful postoperative management are necessary to achieve satisfactory results.

Summary

A study of long-term results of a technique for ureterocutaneous anastomosis used in 22 patients reveals the following results: 13 satisfactory, 5 fair, and 4 poor. The primary cause of unsatisfactory results is necrosis, with retraction of the ureteral ends. This may be due to poor surgical technique, inadequate postoperative management with the development of secondary inflammation of the anastomotic site, or undue tension of the ureter. By the use of this technique normal renal function can be maintained over a period of years without the use of ureteral catheters.

122 S. Michigan Ave. (3) (Dr. McDonald).

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1. Heckel, N. J.: Ureteral Cutaneous Anastomosis: Technique to Eliminate Permanent Ureteral Catheters, J. Urol. **54**:430-433 (Nov.) 1945.

ANEURYSMAL BONE CYSTS OF SPINE

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and
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In 1955, a young man with a bone tumor of the spine entered the Indiana University Medical Center and was subsequently found to have an aneurysmal bone cyst of the eighth thoracic vertebra. The similarity between this case and several previous cases designated by the pathologist as giant-cell tumors of the spine seemed to warrant a histological review of all cases so diagnosed at this institution. Dr. Frank Vellios of our pathology department found five patients for whom the original diagnosis was giant-cell tumor of the spine but who, on critical review, were found to have an aneurysmal bone cyst. The material from a seventh case, occurring in a private patient of one of us (J. W. B.), was likewise reviewed, and there was also found to have been an erroneous diagnosis of giant-cell tumor. These seven cases compose the study group and will be considered from their roentgenologic aspects.

From the Department of Radiology, Indiana University School of Medicine.

Read before the Section on Radiology at the 105th Annual Meeting of the American Medical Association, Chicago, June 13, 1956.

• *Bony lesions occurring at various levels of the vertebral column in seven young people between the ages of 13 and 28 years were originally diagnosed roentgenologically as benign giant-cell tumor (three cases), benign bone cyst, extramedullary neoplasm, granulomatous lesion, and epidural abscess. The case histories are given in some detail to illustrate the severe pain and disability caused by these lesions and their treatment by surgery and roentgen irradiation. Five of the patients have become asymptomatic. One required a second irradiation because of return of symptoms but continued to improve thereafter; another was improving but had not yet recovered completely when last observed. The lesions in these seven cases were all found, on critical review, to be aneurysmal bone cysts. Diagnosis depends on finding by x-ray a characteristic thin rim of cortical bone about the expanding cyst. The fact that six of these seven lesions had been originally misdiagnosed by pathologists as giant-cell tumors is significant. Exact diagnosis is important because for aneurysmal bone cysts the prognosis is excellent.*

Jaffe and Lichtenstein [1] first described this lesion in 1942, and in 1950 Lichtenstein [2] reidentified this process more precisely as a distinct clinical, roentgenologic, and pathological entity. An increasing awareness of this entity since then,[3] plus correction of erroneous diagnoses (such as we have done), will aid in recognition of this benign bone lesion with such a nebulous pathogenesis.

Clinical Features

The lesion occurs chiefly in children, adolescents, and young adults. The ages of our patients were 13, 13, 17, 21, 22, 24, and 28 years. No predilection was found for either sex. In our experience, the duration of symptoms was short, ranging from three to seven months. All patients complained of pain that gradually became worse; in three patients, there was encroachment on the spinal cord, with resultant paralysis of the lower extremities. Four of these lesions involved two contiguous vertebrae, one a single vertebra, and two were localized in the sacrum. The extent of the lesion, as seen on roentgenograms, did not parallel the degree of symptoms in most cases. Pain, swelling, and limitation of motion usually precede the onset of profound neurological disturbance and afford a chance for diagnosis before irreparable cord damage may ensue. Cord damage is more apt to occur in those instances of osteolytic destruction with collapse of vertebral structure or in lesions expanding the inner aspect of the neural arch.[4]

Pathological Features

Aneurysmal bone cysts are seen to be composed of irregular blood-filled spaces, ranging in size from a few millimeters to many centimeters in diameter, with free communication between these areas. The septums that separate these spaces are composed of long strands of osteoid tissue together with spindle-shaped stromal cells and multinucleated giant cells. Occasionally, a large portion of the mass may be cellular and more closely resemble benign giant-cell tumor. Histopathological diagnosis is not difficult if biopsy is adequate.[5]

Roentgenologic Findings

The roentgenologic diagnosis of aneurysmal bone cyst is more difficult in the spine than in the extremities. It may involve any part of the vertebra but seldom if ever involves more than two adjacent segments of spine. The findings are specific when an expanded cyst-like area can be seen, delineated by a fine, sharply defined rim of periosteal bone.[6] We were impressed with the fact that the thin shell of cortical bone about the periphery of the tumor may be entirely absent in some cases, making roentgenologic recognition elusive. This disruption of peripheral cortex may result from the erosive pressure from neural arch or ribs (cases 3 and 4), and the roentgenograms merely show a destructive process. The lesions involving the neural arch may be particularly vicious in that they may produce no evidence of destruction on the routine roentgenograms [7] and may even require myelography for detection.[8]

The original roentgenologic diagnoses in our cases included extramedullary neoplasm, benign bone cyst, granulomatous lesion, and benign giant-cell tumor (in three cases). In one case (case 4), involving the eighth thoracic vertebra, faint destruction of the left pedicle was evident roentgenographically, and an epidural abscess was suggested. A review of all roentgenograms in this series, however, made us feel that the roentgenologic appearance was specific in five of the seven cases.

Report of Cases

Case 1.—A 13-year-old female was admitted in November, 1941, complaining of pain between the shoulders and in the neck. For the past five months she had had pain in her arms. Two months prior to admission she had fallen, striking her head and neck. Since that time she had noted weakness and finally paralysis of the lower extremities. Roentgenologic examination (fig. 1) revealed almost complete destruction of the spinous process and laminas of the seventh cervical vertebra. Some collapse of the spine and a kyphotic deformity were present at this level.

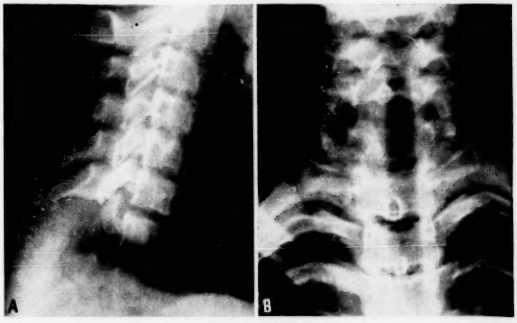

Fig. 1 (case 1).—Aneurysmal bone cyst of cervical vertebra. *A*, lateral view, showing lysis of posterior neural arch of C-7, with thin rim of expanded bony cortex faintly visible in region of the spinous process. *B*, anteroposterior view, showing destruction of spinous process, lamina, pedicles, and part of articular processes.

A pathological diagnosis of atypical giant-cell tumor of bone was made. Roentgen therapy was administered, with 1,200 r in air, a 10-by-7-cm. portal posteroanteriorly, given in two weeks. (All therapy was 250 kv. with 0.5 mm. Cu—1 mm. Al filtration unless otherwise specified.) This was repeated one month later, after the flaccid paralysis had changed to a spastic paralysis. Four months after x-ray therapy, a complete bilateral laminectomy was performed on the sixth and seventh cervical segments and the first two thoracic segments. There was complete return of motor and sensory functions, with no roentgenologic evidence of recurrence of the tumor. Roentgenograms 15 years later revealed firm bony union of the lateral bone grafts across the segments. The patient is asymptomatic.

Case 2.—A 13-year-old female was admitted in February, 1948, with pain in her right knee and hip of three months' duration. The pain followed an accident in which a ball struck her knee. Two months prior to admission the patient began to complain of backache, which became progressively worse. Physical examination revealed right lumbar muscle spasm. There was tenderness over the first, second, third, and fourth lumbar vertebrae on the right of the spine. Right straight-leg raising and double straight-leg raising were painful. The reflexes were normal.

Roentgenologic examination of the lumbar spine (fig. 2) revealed a rounded, cystic, asymmetrical, expanding lesion, involving the body, lamina, pedicle, and transverse process on the right side of the third lumbar segment, and a smaller lesion involving the right superior articular facet of the second lumbar vertebra. At surgery, a tumor measuring roughly 8 by 5 cm. was removed from the lumbar vertebrae. The tumor had destroyed

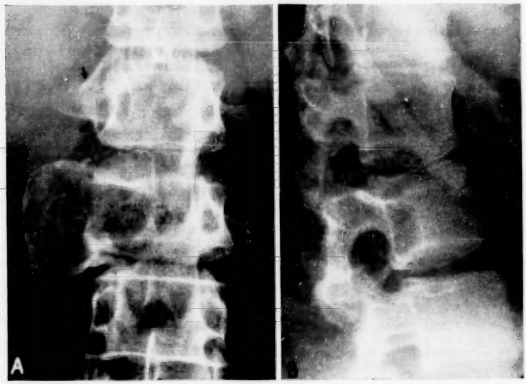

Fig. 2 (case 2).—Aneurysmal bone cyst of lumbar vertebra. *A*, definite cyst-like expansion of cortices of right lateral aspect of neural arches of L-2 and L-3. *B*, lateral view illustrates involvement of vertebral body, pedicle, lamina, and transverse process of L-3 and pedicle of L-2.

the lamina, spinous process, and transverse process of L-3 on the right and portions of L-2. The histopathological diagnosis at that time was benign giant-cell tumor.

Roentgen therapy was administered, with 2,500 r in air, 12-by-7-cm. portal posteroanteriorly, given in two weeks. Three months later the patient was given a second series, totaling 1,800 r in air to the same portal in 10 days, to alleviate pain. After one year the patient was asymptomatic. Roentgenologic examination eight years later, in May, 1956, demonstrated no recurrence of the lesion.

Case 3.—A 17-year-old female was admitted in February, 1945, with a history of pain and swelling in the right side of the neck for five months. The pain radiated down the right arm. Physical examination revealed tenderness and swelling over the right side of the neck. No pain was elicited with pressure over the bodies of the cervical vertebrae.

X-ray studies of the cervical spine revealed partial destruction of the fourth and fifth cervical bodies and almost complete obliteration of the intervertebral disk between these structures. There appeared to be an indefinite soft-tissue mass anteriorly and below the involved bodies. A biopsy of the cervical vertebrae was obtained, and the diagnosis was reported as a giant-cell tumor of bone.

Roentgen therapy was administered, with 1,600 r in air, 10-by-8-cm. portal posteroanteriorly, given in two weeks. Two months later 1,600 r in air was again given, but to a lateral 10-by-8-cm. portal.

Roentgenograms taken three months later revealed no increase in the deformity of the vertebrae involved. There was evidence of considerable calcification in the soft tissues to the right and anteriorly between the fourth, fifth, and sixth cervical vertebrae. An 11-year follow-up in May, 1956, demonstrated continued improvement, but some residual deformity was still present. The patient was asymptomatic.

Case 4.—A 22-year-old male was admitted in November, 1955, with a history of pain in the midthoracic spine for four months. The pain was not severe but had continued intermittently. One week prior to admission he became unable to defecate, and four days prior to admission he became incontinent and paralyzed in the lower extremities. Roentgenograms of the thoracic spine (fig. 3) showed rarefaction of the pedicle and lamina of T-8 on the left. An epidural abscess was suggested by the radiologist. At surgery, a vascular, granulomatous lesion that involved the laminas of the seventh and eighth thoracic vertebrae was found. A histopathological diagnosis of aneurysmal bone cyst was made. X-ray therapy was given, with a total dose of 2,500 r in air, 10-by-8-cm. portal posteroanteriorly, in 12 days.

In May, 1956, at the time of discharge, the patient was able to walk about on crutches and had good control of his bowel and bladder. Roentgenograms showed no recurrence. Minimal residual neurological findings were present at this last examination, and the patient reported continued improvement.

Case 5.—A 24-year-old female was admitted in November, 1954, after surgery elsewhere for a tumor of the first and second thoracic vertebrae. The original diagnosis was benign giant-cell tumor, but a review of pathological sections confirmed the impression of aneurysmal bone cyst. The patient had experienced motor palsies of the lower extremities and continued to have back pain after the initial surgery. Roentgen therapy (1,000 kv.) was administered, with 3,150 r in air, 8-by-6-cm. portal posteroanteriorly, given in two weeks. Definite improvement was noted until January, 1955, at which time signs of nerve-root involvement were again seen. Repeat therapy was given, consisting of 1,600 r in air, 10-by-8-cm. oblique portals, in 16 days. Continued improvement was noted in May, 1956.

Case 6.—A male, aged 28, was admitted in January, 1942, with a history of severe pain in the left leg of seven months' duration, with moderate pain in the lower part of the spine. Roentgenograms demonstrated a large area of destruction involving the greater portion of the lower three sacral segments, leaving only a thin rim of bone on the right lateral and posterior aspects. The tumor was partially resected at another hospital in October, 1941. Further resection was necessary in January, 1942. X-ray therapy was given after surgery and repeated in two months with 1,200 r in air, 10-by-8-cm. portal posteroanteriorly, given in six days. Progressive improvement was noted, and in May, 1956 (14-year follow-up), the patient was asymptomatic with no roentgenologic evidence of recurrence.

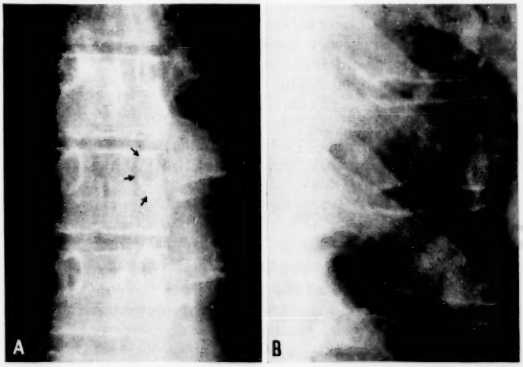

Fig. 3 (case 4).—Aneurysmal bone cyst of thoracic vertebra. *A*, anteroposterior view, demonstrating thinning of cortex of pedicle on left side of T-8. *B*, lateral view, showing slight rarefaction of margin of pedicle and suggestion of some expansion of its cortex. Roentgenologic appearance is not specific.

Case 7.—A 21-year-old male was first seen in November, 1936. He complained of pain in the lower part of the back and down the right leg of moderate severity. Roentgenograms (fig. 4) revealed a large "fibrocystic tumor involving the right sacrum, probably giant cell tumor." Biopsy confirmed the radiologist's impression, and roentgen therapy was given to the

sacral area with a total of 865 r in air (200 kv. 0.5 mm. Cu—1 mm. Al), 10-by-10-cm. portal posteroanteriorly, given in three days. This was repeated in two months, the total dose being 1,730 r in air. Postradiation films showed improvement in the appearance of the lesion, with definite filling-in of the lytic lesion by new bone. When last seen, in 1944, eight years after treatment, the patient was asymptomatic; roentgenograms showed considerable improvement. Review of histological material showed the lesion to have been an aneurysmal bone cyst.

Comment

The etiology of aneurysmal bone cyst is unknown, and we are unable to assign any importance to trauma, which has been suggested as an etiological agent.[7] In the spine, aneurysmal bone cyst is found more frequently in the neural arch or in the transverse or spinous processes. The sacrum also seems a fairly common site.

In 1941, one of us (J. A. C.), using roentgen therapy, treated a destructive osteolytic lesion of the neural arch of the seventh cervical vertebra (case 1). This process had been cautiously designated by the pathologist as atypical giant-cell tumor. Since it was thought desirable to decrease the vascularity of the lesion to allow further surgery, and since roentgen therapy for other types of giant-cell tumors was popular at that time, 1,200 r in air was administered over the lower cervical spine in two weeks. The prompt regression of the mass and of the flaccid paralysis led to a repetition of the roentgen dosage, and at the time of laminectomy, four months later, very little of the lesion was found. The patient made an uneventful recovery with no neurological defects.

A repetition of this experience with several similar vertebral lesions during the next decade led to the supposition that this vascular type of giant-cell tumor was unusually radioresponsive but that such treatment was frequently enhanced by partial surgical resection. Roentgen therapy was administered through one or two portals covering the involved spinal segments from the posterior and lateral aspects.

All of our seven patients received x-ray therapy, five in conjunction with surgery and two after surgical biopsy only. Therapy was usually given in two series of 1,200 to 1,600 r in air about one to two months apart. No minimum dosage for optimal results was established, but it is suspected that a single series of roentgen therapy, over the involved area, of 1,600 r in air in two weeks might well suffice as a preoperative measure or for those lesions that are inaccessible to excision. The rate of regression differed, being fairly rapid in some and slow in others, but five patients recovered completely and two (cases 3 and 5) satisfactorily. The patients in cases 1, 2, 4, 6, and 7 showed rather complete regression of roentgen findings, while those in cases 3 and 5 still showed less than complete regression six and two years, respectively, after therapy.

In our experience, there have been no late untoward effects of radiation. In May, 1956, six of our patients were recalled for a follow-up of 1, 2, 8, 11, 14, and 15 years, respectively, covering both clinical and roentgenologic studies. Continued regression and healing of bone defects was noted in every instance. We feel that this is important because Lichtenstein [2] and Dahlin and co-workers [6] caution against overirradiation, and each reports one instance of postirradiation sarcoma. Our studies suggest an excellent prognosis for this benign condition, even though the disease tissue was obviously incompletely removed surgically or destroyed by radiation.

The differential diagnosis of aneurysmal bone cyst and benign giant-cell tumor of the spine can readily be made by the pathologist. Roentgenologically, benign giant-cell tumors rarely involve the spine and are usually seen in patients beyond 20 years of age. They recur readily, their response to radiotherapy is erratic, and some become malignant. Aneurysmal bone cysts, on the other hand, have a uniformly good prognosis, do not recur, and respond well to curettage, excision, or roentgen therapy.

Summary and Conclusions

Aneurysmal bone cysts occur not infrequently in the spines of children and young adults. Etiology is unknown. Six of our seven patients had been given a histological diagnosis of giant-cell tumor of the spine, and, upon recent review of these pathological sections, all of these were redesignated as aneurysmal bone cysts. The roentgenologic diagnosis can be made with considerable specificity when the cystic expansion of bone occurs with the characteristic thin, peripheral rim of cortical bone. This was true in five of our seven cases. Roentgen therapy, in conjunction with partial surgical resection, was successful in the treatment of this small series of patients. Six patients were reexamined clinically and with repeat x-ray studies within two months of this report. Continued regression or complete healing of the bone defects was noted in every instance.

Fig. 4 (case 7).—Aneurysmal bone cyst of sacral vertebra. *A*, film taken in 1936, showing multilocular lysis and expansion of right half of first and second sacral segments, with thinned peripheral rim of cortical bone. *B*, film taken in 1944, eight years after roentgen therapy, showing considerable osseous repair of lesion and regression of cystic changes.

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EARLY USE OF ANTICOAGULANTS IN TREATMENT OF MYOCARDIAL INFARCTION

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• Series of patients with myocardial infarction treated with anticoagulants have generally shown a decrease in death rate of one-third to one-half that seen in series of such patients on other types of treatment. The incidence of thromboembolic complications has been more strikingly reduced. Contraindications and caution must be observed with anticoagulant therapy is used, and laboratory facilities must be adequate to measure its effect on the blood. For rapid action, 1,200 to 1,500 mg. of ethyl biscoumacetate and 200 to 300 mg. of bishydroxycoumarin are given at the same time by mouth; thereafter the bishydroxycoumarin is given daily in doses, generally of between 25 and 50 mg., that will maintain the prothrombin time between 22 and 35 seconds as determined by the Quick one-stage method. In some patients it is desirable to give heparin, 75 mg. subcutaneously at 12-hour intervals for two or three doses. The anticoagulant effect of the coumarin and indanedione compounds can be terminated promptly if necessary by the use of phytonadione (vitamin K_1). It is frequently difficult to classify attacks of myocardial infarction as severe or mild during the early days of the attack. The decision as to which patients should receive any form of therapy must rest on the judgment of the physician.

The use of anticoagulant substances in the treatment of myocardial infarction is now widely accepted throughout the civilized world.[1] They have been used successfully in large medical centers, and, of equal importance, in those small communities where there exists the fortunate combination of a well-trained, conscientious physician; a good laboratory capable of performing accurate prothrombin tests; and an intelligent, cooperative patient.[2] The favorable early reports were confirmed by the comprehensive report of the committee on anticoagulants of the American Heart Association[3] and have now been substantiated by more than 40 reports from institutions in the United States and numerous foreign countries. These reports have demonstrated that workers in many areas, working under a variety of conditions, can obtain a marked reduction in the death rate and an even more striking reduction in the rate of thromboembolic complications by the use of anticoagulants. Three recent papers of especial interest are those of Gilchrist and Tulloch[4] of Scotland, Holten[5] of Denmark, and Glueck, Ryder, and Wasserman[6] of the United States. The reduction in the death rate has been remarkably consistent, considering the widely varying circumstances under which the studies have been conducted and the differences in the criteria used for the diagnosis of acute myocardial infarction. Almost without exception, the series of patients treated with anticoagulants have shown a decrease in the death rate of approximately one-third to one-half that in the control series. There have been a few dissenting opinions, but most of the objections have been based on opinion rather than on actual experience with the use of these drugs.[7] There have been a very limited number of reports that have not confirmed the usual finding.[8] In several of these the authors themselves have pointed out inadequacies in the laboratory or clinical handling of their cases.

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It should also be emphasized that for this type of study series of less than 250 cases do not usually provide statistically valid material.

Thromboembolic Complications

It is clear that, while a reduction in death rate is a most desirable goal in this type of treatment, it is not the only one. It is also important to prevent such additional thromboembolic complications as the development of new thrombi in the arterial system; the growth of mural thrombi within the chambers of the heart with resulting emboli to the lungs, brain, extremities, and peripheral arteries; and the development of venous thrombi, which are especially apt to occur in the legs and pelvis during inactivity and which are

major sources of pulmonary emboli. All of these complications are common after myocardial infarction. Frequently their effects are of major significance and are easily recognized; at other times they are more subtle, and a positive diagnosis cannot be established during the patient's life. The question arose as to whether those who were interested in the subject were overdiagnosing these complications. However, pathological studies on patients on whom autopsies were performed have shown that the contrary was true: More thromboembolic complications existed in control patients than had been diagnosed clinically, and this was true to a lesser degree with the patients treated with anticoagulants.[3]

Other facts of interest were found at autopsy.[3] There was no difference between treated and untreated patients in the number of new infarcts or extensions found: in both groups there were 27 complications per 100 patients. Mural thrombi were found in 30 of 48 control patients, or 62.5%. In contrast, of 41 patients treated with anticoagulants, mural thrombi were found in 13 (31.7%). The prevention of mural thrombi has a long-range as well as an immediate significance, since these thrombi may remain pocketed in the heart chambers for many years and represent a threat of embolization. Towbin[9] demonstrated pathological evidence of multiple cerebral embolism in 11 patients who had old myocardial infarctions, in some cases several years prior to the cerebral emboli. All of the patients had harbored intracardiac mural thrombi.

Extracardiac thromboembolic complications were found as follows: Of 48 control patients, only 8 (16.7%) were thought, clinically, to have complications, but 21 (43.7%) were found to have such complications at autopsy. Of 40 patients treated with anticoagulants, 4 (10%) were thought to have extracardiac thromboembolic complications, but 11 (27.5%) were found to have such complications at autopsy. With multiple emboli considered, the average number of such complications per patient was 1.25 for the control group and 0.45 for the treated patients.

Pulmonary emboli were found in 23% of 48 control patients but in only 8% of the 40 treated patients. Some emboli were multiple, and the figures may be presented as 38 pulmonary emboli per 100 patients in the control series as against 10 per 100 of those who had received anticoagulants. Thirty-one emboli to the kidneys were found per 100 control patients, as against 6 per 100 in the group of treated patients. These data certainly were not subjective clinical findings; nevertheless, it was considered desirable that a larger series of cases be subjected to this type of study. This has been done by Gilchrist and Tulloch[4] in a recent paper. While their figures do not coincide exactly in each category with those presented here, the trend is the same. Of 160 control patients on whom autopsy was done, they found pulmonary infarcts in 27 (16.9%), as against 3 instances among 88 treated patients who died, an incidence of only 3.4%. The report by Glueck, Ryder, and Wasserman[6] of the findings in the autopsies of 151 patients includes similar findings and conclusions. The use of anticoagulants seems, therefore, to be well established.

When the results of these experiences are analyzed, it seems evident that, if a patient suffers from a definite myocardial infarction, if there are no contraindications, and if good facilities are available, he should receive anticoagulant therapy. The majority of experienced cardiologists who have also had extensive experience with anticoagulant therapy now agree with this position. At the World Congress on Blood Coagulation, held in Basel, Switzerland, in 1954, a panel from eight countries of 11 workers distinguished in this field agreed unanimously that, unless contraindications exist, all patients should receive anticoagulant therapy. They also agreed that any attempt to withhold the treatment, unless there were some complications, was fraught with a risk that, although statistically small, was often hazardous for the future of the individual patient.[1] An evaluation of the status of long-term anticoagulant therapy is not within the scope of this paper. Favorable reports are appearing from throughout the world.[10]

Selection of Patients for Treatment

The selection of the patients for treatment with anticoagulants depends on a number of factors, including the condition of the patient and a history of any diseases capable of producing easy bleeding, such as acute peptic ulcer, hemorrhagic blood dyscrasias, or malignant hypertension. Recent surgery of the nervous system and surgery that left wide, oozing surfaces, as a prostatectomy does, are definite contraindications. Complete lists of contraindications have been published.[3] The use of the anticoagulants must also depend on convenience and proximity to satisfactory facilities. Ten years ago such facilities, including physicians familiar with this therapy, were very rare; five years ago they were still widely scattered; today they are much more generally available, and their quality has markedly improved.

A few workers, particularly Russek and Zohman,[11] have taken the position that cases should be divided during the first day into mild or "good-risk" cases and severe or "poor-risk" cases and that in the good-risk cases anticoagulant therapy should not be given. The argument to support this is that good-risk patients have such a favorable prognosis and are so free from thromboembolic complications that anticoagulant therapy is not needed. It is said further that anticoagulant therapy is more dangerous than the risk of thromboembolic complications. This position is an inviting one and has been welcomed by many physicians because it relieves them of the responsibility of carrying out the meticulous regimen of anticoagulant therapy. However, the following points should be considered.

Dangers of Hemorrhage.—The dangers of hemorrhage from anticoagulant therapy have been stressed as a reason for not using it in good-risk patients. The evidence for this danger has been based on deaths that have been reported after the use of anticoagulants. However, the figures used are not pertinent to properly controlled therapy because (1) they were obtained during the early period of the use of these drugs, when many inexperienced persons were using anticoagu-

lants; (2) they included cases in which anticoagulants were administered without any prothrombin times being determined; and (3) they included cases of self-medication and, in some cases, self-destruction by administration of these substances.

As further argument against the use of anticoagulants, figures for hemorrhage have been quoted out of context from the report of the committee on anticoagulants. These included hemorrhage in the total series, so that hemorrhage in the severe cases is presented as a reason for avoiding the use of anticoagulants in the mild cases. Hemorrhage is more common in patients with severe cases, whether they are treated with anticoagulants or not. One would expect this with hemopericardium, rupture of the myocardium, and congestive failure. In the mild cases, the incidence of hemorrhage was one-sixteenth that in the severe cases. Actually, only one patient died of hemorrhage as a result of cardiac rupture. This was an 84-year-old woman with hypertension who was listed as severely ill by the admitting physician; she did not show Dr. Russek's signs for poor-risk patients and would, therefore, have been listed as a good-risk patient. This one death occurred in a total of 589 treated cases, 100 (17%) of which were mild, and this hardly seems sufficient evidence to justify the position that the danger of hemorrhage in the good-risk patient was of serious importance in that series. In both treated and untreated patients the incidence of hemorrhage has been extremely low under favorable conditions. Recent reports indicate significant bleeding in from 2 to 3% of patients and deaths from hemorrhage in less than 0.5%. Poor technique is no more to be condoned in this form of therapy than in any other.

Serious thromboembolic complications occur often enough in mild cases to be a constant threat. Twenty-eight such complications occurred in each 100 good-risk control patients in our series.[3] We have seen numerous patients in whom the first recognized evidence of illness was an embolus to the leg, a hemiplegia, or a pulmonary infarct. Electrocardiographic studies of such patients have revealed that they had suffered so-called silent myocardial infarctions, so mild as to be unrecognized, yet capable of leaving the patient crippled for life. Most experienced physicians have known patients who have had so-called mild indigestion or slight angina but who suddenly died when an extension of the infarction or an embolus occurred. Many of these could only be classified as having mild or good-risk cases. If such cases can result in serious complications and death, then all degrees of recognizable infarction can do so. DeFrancisco and I [12] have reported 14 patients with such "mild cases." These 14 patients developed 18 certain and 4 probable thromboembolic complications. In this series four had major amputations; one of these died after a series of thromboembolic complications; one had a minor amputation; the remainder had serious cerebral emboli or pulmonary emboli.[12]

Several workers have attempted to follow the classification of Dr. Russek but found that they were forced to reclassify from 25 to 35% of the cases within four days.[13] It is sometimes too late after the first embolus has occurred. A man may recover from his myocardial infarction to live for some years as an amputee or with hemiplegia, but there is little satisfaction for the physician in such an outcome. Holten [5] of Denmark has recently analyzed the possibility of applying such criteria to early myocardial infarction and has found that this resulted in an error in evaluation in 22% of his cases. I agree that there are all degrees of myocardial infarction, but, while the death rate and even the complication rate of mild cases is statistically relatively low, the only sound time to classify an attack as "mild" is after the patient has been discharged from the hospital at the end of three or four weeks.

The figures presented by Russek for his good-risk cases show far lower rates of complication than those of most published reports. He also classifies a much larger percentage of his total patients with myocardial infarction as good-risk patients than do most others. For example, he lists approximately 60% as good-risk patients, whereas in the anticoagulant committee study only 17% were considered to be in that category. A probable explanation for this great divergence lies in a marked difference in the manner of diagnosis, selection, and study of the cases. Russek states that the cases included in his series are all "documented cases," but does not define specifically what this means. It is clear that cases are included that would have been considered doubtful had stricter criteria been used. [3] Such cases would naturally have a better prognosis from the viewpoint of both complications and death rate, but the committee did not include them since they did not seem valid in an effort to evaluate the effects of anticoagulants in myocardial infarction.

Newer Anticoagulants

As I predicted a decade ago, once the effectiveness of this form of therapy was established, a variety of new anticoagulants and allied substances has been made available.[14] Ethyl biscoumacetate (Tromexan ethyl acetate), cyclocumarol (Cumopyran), 3-(1-phenylpropyl)-4-hydroxycoumarin (Marcumar), warfarin sodium, and other coumarin derivatives are all effective and act similarly to bishydroxycoumarin (Dicumarol), although they have different rates and durations of action. Phenindione, representing another chemical group, has been followed by several derivatives that are equally effective. Heparin sodium still stands alone as the one compound of its group that is satisfactory. Paritol and Treburon have been shown to be too toxic for use. Phosphorylated hesperidin acts like heparin sodium but does not have the advantages of activating a co-factor. It deserves additional study and attention. Crystalline trypsin is ineffective and often irritating in doses that appear to have no therapeutic value. Plasmin has a potent enzymatic action that produces dissolution of thrombi at a rapid rate. This substance has thus far had limited therapeutic use. It has proved difficult to standardize different lots of plasmin, but it is worthy of wider trial for evaluation.

Technique of Administration.—All of the coumarin and phenindione derivatives mentioned here may be used effectively by a physician who is experienced with them and their action. There is no evidence that

the death or complication rate due to the underlying disease varies as a result of the use of one as against the others, but large, well-controlled series have not been published to establish this point. If a patient with myocardial infarction has had no evidence of recent emboli and is not extremely ill, the following regimen is suggested.

In order to obtain rapid action, 1,200 to 1,500 mg. of ethyl biscoumacetate and 200 to 300 mg. of bishydroxycoumarin is given at the same time. Thereafter, bishydroxycoumarin is given daily, the dosage being regulated according to the Quick one-stage method; the desirable therapeutic level is between 22 and 35 seconds with a control level of 15 seconds. The average dose of bishydroxycoumarin necessary to produce this is 75 mg. daily, but it may vary from 25 to 150 mg., and daily tests are thus required until the average requirement for each patient is determined. Thereafter, the time between tests may be gradually increased until they are performed once a week. If the patient is acutely ill, and especially if he has had recent evidence of thromboembolic complications, it is advisable to initiate treatment by administering 75 to 100 mg. of heparin sodium subcutaneously at 12-hour intervals for two doses. The first dose should be given at the same time as the ethyl biscoumacetate and bishydroxycoumarin. The chief reason for continuing the treatment with bishydroxycoumarin instead of ethyl biscoumacetate is one of expense, since the former drug is much less costly. Because many of these patients, especially those who have had their second or third attacks, are now maintained on long-term therapy, it is wise to establish them on the less expensive and equally satisfactory bishydroxycoumarin. Some of the coumarin compounds are longer-acting than bishydroxycoumarin, but there is little gained by taking a drug twice a week rather than once a day unless it has some striking advantage either therapeutically or financially. In fact, it is more apt to be forgotten because of lack of a regular habit.

The shorter-acting drugs such as ethyl biscoumacetate have now only the advantage of rapid initial action, since the action of the long-acting ones can be terminated promptly by the use of phytonadione (vitamin K_1). This substance has added greatly to the safety of anticoagulant therapy. While it may be given intravenously, it is practically as satisfactory administered orally. The following technique is suggested: If the prothrombin time reaches 60 seconds or more without bleeding, give 10 mg. of phytonadione in tablet form or, if liquid, in orange juice. If it is above 80 seconds or if there is gross bleeding, give 20 mg. This will usually produce a definite drop in the prothrombin time within three to six hours. If it does not, the dose may be repeated. Even with much higher prothrombin times this dose will usually be effective. With this technique, serious bleeding is almost entirely eliminated. Long-term patients should keep a small supply on hand and, if they notice gross bleeding, take 10 mg. and call their doctor. The need for whole-blood transfusions for bleeding has been markedly reduced as a result of the availability of phytonadione.

Comment

In this paper practical points have been emphasized rather than experimental and statistical studies. The report of the committee on anticoagulants and many others are available for the reader's reference. The decision as to which patients should receive any form of therapy must rest on the judgment of the physician. His decision, however, should be based on all available facts. It is hoped that this brief outline will aid physicians to come to sound conclusions regarding this form of therapy.

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LIMITED USE OF ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

ANALYSIS OF ONE THOUSAND "GOOD-RISK" CASES

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• *Patients with the diagnosis of acute myocardial infarction can be classified as good or poor risks at the time of the first examination. Those who have never had previous infarctions, who do not have intractable pain, extreme or persistent shock, significant cardiac enlargement, gallop rhythm, congestive heart failure, auricular fibrillation or flutter, or ventricular tachycardia or intraventricular block, and who do not have diabetic acidosis or other states predisposing to thrombosis are classified as good risks. Data previously reported are here supplemented by data from 511 good-risk patients who did not receive anticoagulant therapy and were closely watched for thromboembolic complications. The latter occurred in only 3.7% of the cases and all were of a mild nature. There were 18 deaths. Analysis of the causes of death did not yield evidence that anticoagulant therapy would have reduced the mortality to a significant degree. The mortality of 3.5% for the good-risk patients was in marked contrast to the mortality of 60% previously found for poor-risk patients. The authors believe that anticoagulant therapy, which has certain hazards, is neither necessary nor desirable for patients who have been classified as good risks by the above criteria.*

It is part of the natural history of discovery to find that enthusiasm and emotion often outstrip logic. This human failing is no doubt responsible for the prevailing custom of applying a new drug first and evaluating it later. It is true that numerous investigations have confirmed the value of anticoagulant therapy in acute coronary occlusion. Nevertheless, after eight years of extensive clinical experience, we have still found no valid evidence to support the contention that all patients with this disease should be treated with anticoagulants.[1] As a consequence of the debate over the effectiveness of this therapy, many practicing physicians today are uncertain whether they are negligent in withholding anticoagulants from patients with relatively mild attacks or imprudent in prescribing them, despite expense, inconvenience, and discomfort, in such cases when no definite service and possible harm may be rendered. Obviously, to resolve this problem one must define clearly the risk of thromboembolism in "good-risk" patients, those who sustain an uncomplicated first attack. The hazard of the complication must then be weighed against the possible benefits and dangers inherent in this form of therapy.

Classification of Patients

In an earlier study,[2] it has been shown from a review of hospital case records that only 3 out of every 100 patients in this good-risk group die during the period of hospitalization and that only one of these fatalities occurs after the first 48 hours of admission. It was demonstrated further that the clinical incidence of thromboembolism in this selected group is less than 1%. These favorable results were in distinct contrast to the findings in the "poor-risk" category, in which the mortality rate was 60% and the incidence of thromboembolism 10.6%. In view of the reported incidence of hemorrhagic complications from anticoagulant therapy even in the hands of the most competent investigators, it was concluded that, although treatment with anticoagulants appears warranted in patients manifesting poor prognostic signs, there is no justification for its use in patients who qualify as good risks at the time of their first examination.

Similar observations and conclusions have been reported in such various independent studies as the series of Papp and Smith [3]; Baer, Heine, and Krasnoff [4]; Littmann [5]; Furman and associates [6]; and Schnur.[7]

Nevertheless, to test the validity of these findings, Wright [1d] has reexamined the data of the committee on anticoagulants and has analyzed their collective experience with regard to good-risk patients. He has reported that only 17% of the total series could be classified in this category and has implied that the low-risk group represents only a small proportion of the patients hospitalized for myocardial infarction. In sharp contrast, however, other studies indicate that such cases comprise almost half of all hospital admissions for this disease.[8] Consequently, it seems more likely that the low incidence of good-risk cases in the committee's study resulted from the careful "screening" prevalent in teaching and research hospitals, which permits only the patients with more serious or interesting cases to gain admission. On the basis of this very limited experience comprising 24 patients in the control group and 47 in the treated group, Wright [1d] has reasserted the need for anticoagulant therapy even in patients sustaining the mildest attacks. He as well as others [9] has challenged the validity of data derived from retrospective studies of hospital case records, contending that it is much more difficult to classify patients prognostically at the onset of an attack than in retrospect after their discharge from the hospital. The findings in the present study however, attest to the feasibility and justification of

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such classification at the onset of the attack or early in its course to determine the need for anticoagulant therapy.

Early Prognosis.—Some observers have insisted that it is impossible to determine with certainty the prognosis of an acute myocardial infarction during the first 24 or 48 hours. To substantiate this view they refer to the report of Halpern and associates,[10] who found that it was necessary to change the prognosis in 29% of a group of patients during the first 48 hours of hospitalization. Critical analysis of this report, however, reveals the following fallacies in the conclusions drawn concerning good-risk cases. The authors state, "The estimation of the prognosis was purely an uninstructed personal opinion of the doctor handling the case." Thus, with no uniformity in criteria six out of an unstated number of so-called good-risk patients were transferred to the poor-risk category during the first 48 hours. The significance of this observation is further obscured by the authors' statement that 11 patients had to be reclassified in retrospect because previous myocardial infarction and heart failure had not been utilized as signs of poor prognosis. The effect of this major adjustment in classification on the statistics that reflect the accuracy of the initial prognosis is not revealed. Thus, no conclusions can be drawn from this study regarding subsequent prognosis in those initially classified as good risks on the basis of acceptable criteria.

Anticoagulants in Mild Attacks.—The question of whether anticoagulants should be administered to patients with mild attacks cannot be answered by selected case reports. Such attempts merely dramatize the danger of thromboembolism on the one hand or of hemorrhagic complications on the other, without providing insight into the relative risks involved. De Francisco and Wright[11] have recently recorded the occurrence of thromboembolic complications in 14 so-called good-risk patients suffering from myocardial infarction who were untreated or inadequately treated with anticoagulants. It is noteworthy that, of these 14 cases, 9 represented instances in which silent infarction had occurred or the diagnosis had been overlooked. In none of these nine patients, therefore, was restricted activity or bed rest imposed at the onset of the attack. Obviously, a patient who continues normal activities while harboring a fresh myocardial infarction, however mild, is more likely to develop all the complications that may arise in this disease. There not only is a greater likelihood of thromboembolism but also of congestive heart failure, shock, arrythmias, cardiac rupture, and sudden death. Consequently, the observations of De Francisco and Wright point up the need for restriction of activity even in the mildest case rather than the establishment of anticoagulant therapy. At least two of the patients in their series, moreover, could not be classified as good-risk patients according to criteria previously enumerated.[2] It is also of interest to note that it was necessary to go back 22 years to obtain one of the cases in their report. Most physicians would agree that if anticoagulant therapy in its present form and manner of control had been in existence for that period of time little difficulty would be encountered in assembling an impressive series of cases in which serious hemorrhagic complications occurred in good-risk patients during the course of anticoagulant therapy.

Reference is frequently made to the opinions of panels of authorities with regard to the indications for anticoagulant therapy in acute myocardial infarction.[11] These opinions have varied from unanimous agreement that all such patients should be treated in this manner to similar unanimity of opinion that only selected patients manifesting serious signs and symptoms warrant this form of therapy. It would indeed be of distinct advantage if scientific problems could be resolved in this manner. Unfortunately, such polls of authoritative opinion, while interesting and provocative, not only do not afford a definitive answer but often take on the spurious aspect of factual evidence.

Analysis of Cases

In order to determine the mortality rate and incidence of thromboembolism in good-risk patients not receiving anticoagulant therapy, we have analyzed the clinical course of 1,000 patients who at the time of their first examination after the onset of their attacks fulfilled the necessary requirements for such classification.

Composition of Sample.—The series of 1,000 cases was derived from two groups of patients that differed only in the manner in which their clinical course was followed. The first group consisted of 489 patients who were classified and studied in retrospect, long after their discharge from the hospital. In selecting these cases we considered only the facts in the history and physical examination that were available on the first day of admission to the hospital. A study was then made of the clinical course and subsequent outcome in each case. Inasmuch as selection was independent of the data recorded in the histories after the first day of admission and was made without knowledge of the final result in each instance, the element of bias is believed to have been excluded. The results of analysis in this group have already been reported.[2]

To test the validity of these findings, we have collected data reflecting the clinical course in a second group of 511 good-risk patients who were carefully followed and scrutinized for thromboembolic complications from the time of their first examination to the termination of their confinement. Their ages ranged from 32 to 80 years with a mean age of 56.2; 30% of the patients were 60 years of age or older. The ratio of males to females was 3.2:1.

Of these 511 patients, 248 were treated and observed daily by us in hospital wards or in private practice. The 263 additional patients in the survey were under the care of collaborating physicians, all qualified internists, and were managed in identical fashion. In the latter group, 138 patients were seen in consultation by us while 125 did not come under our direct observation. The criteria used to establish the diagnosis of acute myocardial infarction and to identify the good-risk patient were clearly defined and uniformly maintained throughout the study. Only cases with typical

clinical onset and classic electrocardiographic patterns were selected for this investigation. Unequivocal electrocardiographic evidence of transmural infarction was commonly observed among the patients comprising the series. Since abnormal Q waves were a prerequisite for diagnosis, patients with intermediate coronary syndromes were not included. Similarly, cases in which a doubt existed regarding the presence of a recent myocardial infarct were rigorously excluded from the series. Of the 511 patients, 128 were treated at home and 383 were hospitalized.

Approximately 70% of the patients were first observed on the day of the attack; in every case clinical diagnosis of acute myocardial infarction was confirmed by one or more electrocardiograms. As in the previous investigation, a good-risk patient was defined as one who manifested none of the following poor prognostic signs at the time of the first examination: (1) previous myocardial infarction; (2) intractable pain; (3) extreme degree or persistence of shock; (4) significant enlargement of the heart; (5) gallop rhythm; (6) congestive heart failure; (7) auricular fibrillation or flutter, ventricular tachycardia, or intraventricular block; and (8) diabetic acidosis or other states predisposing to thrombosis. All patients were treated conservatively with an average period of bed rest of three to four weeks. Chair treatment was frequently instituted after two weeks, but the bedside commode or bathroom privileges were allowed after the first few days. Mild activity in bed and leg exercises were encouraged from the onset. Evidence of thrombotic complications was sought in intensive and frequent physical examinations, urinalyses, blood cell counts, and electrocardiograms and serial roentgenograms in patients developing chest pain.

Mortality and Incidence of Thromboembolism in Good-Risk Cases of Acute Myocardial Infarction

	Cases, No.	Mortality Rate			
		Over-all, %	After 48 Hr., %	Preventable, %*	Thromboembolism, %
Group 1	489	3.1	1.7	1.0	0.8
Group 2	511	3.5	1.8	0.8	3.7
Average	...	3.3	1.7	0.9	2.3
Total	1,000	...	...	...	...

*% of deaths theoretically preventable if anticoagulants had been used.

Results.—In the 511 patients from whom anticoagulants were withheld because of the mild nature of the clinical picture of their conditions (group 2), there were 18 deaths, a mortality rate of 3.5%. This figure is quite similar to the fatality rate recorded in the earlier study of hospital case records (group 1). The incidence of death after the first 48 hours following admission was also similar in the two groups. The two series showed significant difference only with respect to the clinical incidence of thromboembolism (see table). Although these findings confirm the view that the incidence of thromboembolism is related to the index of suspicion, they also indicate that only the mildest episodes had been overlooked in the earlier study. In the 511 patients in whom every effort was made to discover thromboembolic complications, 9 of 20 of these episodes were presumed merely on the basis of calf tenderness. In an additional five patients mild thrombophlebitis occurred, with pulmonary embolism in one. In three other patients mild symptoms followed embolism to the lung, and in two additional cases this diagnosis appeared probable. None of these patients died. Moreover, in these 511 good-risk cases, not a single instance of cerebral or peripheral arterial embolism was encountered. Consequently, little basis for the use of anticoagulants could be found from a consideration of the clinical incidence of thromboembolism in this group.

Accordingly, attention was then directed to the causes of death in good-risk patients to detect possibilities of theoretical benefit from anticoagulant drugs. In the total series of 1,000 patients in this category there were 33 deaths, a mortality rate of 3.3%. However, only 9 deaths might conceivably have been prevented by the effective use of anticoagulant therapy, since 16 deaths occurred unexpectedly during the first 48 hours, 4 were the result of noncardiac causes, and 4 were produced by rupture of the left ventricle. Of the nine presumably preventable deaths, one resulted from cerebral thromboembolism, three were due to recurrent myocardial infarction, and five resulted from unknown causes. Consequently, it must be conceded that the incidence of thromboembolism as a cause of death is well below 1% in good-risk patients.

Comment

Although individual consideration of patients and the treatment of each case according to its own merits are prime ingredients of good medical practice, there is a strong tendency to follow formalized and stereotyped procedures in all cases of coronary occlusion. This approach to therapy has undoubtedly sprung from the traditional but erroneous view that the outcome of acute myocardial infarction is always "unpredictable because of the constant threat of sudden unexpected death even for persons convalescing favorably." [11A] The present study has demonstrated, however, that, on the basis of clinical criteria alone, the practicing physician can achieve a high degree of prognostic accuracy in selected patients. Thus, in 1,000 good-risk patients the over-all mortality rate was only 3.3%, and of those surviving the first 48 hours 98.3% recovered. Since this low-risk group comprises almost half of all cases of acute coronary occlusion admitted to hospital, it must be conceded that there are few other serious conditions in which we can at the onset clinically separate so large a proportion of cases with so encouraging a prognosis.

Although anticoagulant therapy represents an important advance in the management of acute myocardial infarction, evidence is lacking that any benefit can be derived from such treatment in good-risk patients. In the present study, careful observation in 511 patients disclosed an incidence of thromboembolism of only 3.7%. All of these clinical episodes were of a mild nature, and not a single instance of cerebral or peripheral arterial embolism was encountered. Indeed, embolism to the brain occurred in only 1 of the 1,000 patients studied, while embolism to an extremity was not observed. Furthermore, our autopsy

studies have shown that thromboembolism as a cause of death is well below 1% in good-risk cases. This finding agrees with observations at the Mayo Clinic,[11B] which have demonstrated that in unselected cases of acute coronary occlusion about 1 patient of 100 dies from thromboembolic complications.

Hazards of Anticoagulants.—From these considerations, it must be recognized that anticoagulants are afforded little opportunity to exert favorable action in patients manifesting the clinical features of the good-risk group. Moreover, since even with meticulous care these agents may fail to prevent thromboembolic phenomena or may give rise to hemorrhagic complications, any small benefit from their use in such cases is likely to be nullified or exceeded by their hazards. It is significant that hemorrhagic complications occurred in more than 10% of the patients treated by the committee on anticoagulants. After careful consideration of all clinical and autopsy findings in the committee's data, Wright[1c] has estimated that 1.7 deaths per 100 cases resulted from anticoagulant therapy itself. There is no doubt that the frequency of hemorrhagic complications must be considerably less with mild attacks than with serious ones, as emphasized by Wright.[12] Nevertheless, the fact that one death from hemorrhage did occur in the committee's mild group is of some significance, since it indicates an unwarranted hazard in the use of anticoagulants for patients who would not be expected statistically to have thromboembolic phenomena.

Certainly, even greater danger must exist when anticoagulant therapy is carried out by busy practitioners or by specialists in smaller institutions, where the advantages of teamwork are lacking and laboratory facilities are often overtaxed, inadequate, or substandard. One must not lose sight of the important fact that the majority of patients with acute myocardial infarction are treated by general practitioners and not by specialists in research hospitals and that many patients are still being treated at home.

Early Prognosis.—It has been claimed by some that the estimation of prognosis of a given case of myocardial infarction, based on the signs and symptoms present during the first 24 or 48 hours, cannot be made with any degree of certainty. Our studies show that, in the good-risk group, 1 or 2 patients out of every 100 die unexpectedly within the first 48 hours following admission to hospital. Since thromboembolism plays no part in these early deaths, sudden deterioration in the clinical picture within the first few days obviously cannot be prevented by anticoagulant drugs. On the other hand, if the development of poor prognostic signs at any time during the first 48 hours is met by immediate treatment with heparin sodium, the patient will be better protected than if he had been treated with bishydroxycoumarin (Dicumarol) at the time of the first examination. Certainly, the occurrence of serious manifestations at any time should be considered an indication for intensive anticoagulant therapy, but in our experience, as in that of Halpern and associates,[10] such a development after the first 48 hours is decidedly infrequent.

It must be recognized that the results in the present investigation were obtained under management directed at minimizing the likelihood of thromboembolic complications. Most statistics reflecting the incidence of thromboembolism in acute coronary occlusion were compiled before the dangers of rigid inactivity and prolonged bed rest had commanded critical attention. There can be little doubt that the widespread employment of nonmedicinal prophylactic measures has greatly reduced the frequency of this complication in acute coronary occlusion.

Risk of Immediate Hospitalization.—The general employment of anticoagulant drugs in acute coronary occlusion has been associated with another commonly overlooked risk. So that treatment may be instituted without delay, many patients are rushed to the hospital shortly after the onset of their clinical attack, despite the fact that the highest death rate in this disease prevails during the first 48 hours. Since these early deaths are the result of ventricular fibrillation, cardiac asystole, shock, or congestive heart failure and are unrelated to thromboembolism, they almost certainly cannot be prevented by anticoagulant drugs. The attempt to save the small number who may die from thromboembolism after the first week may therefore jeopardize the chances for survival of the much larger segment of coronary patients known to die from other causes during the first two days. For many patients, the experiences of being jostled in an ambulance or admitting office, being subjected to the psychic trauma of a hospital room and bed, being placed in an oxygen tent (often when oxygen is entirely unnecessary), and being repeatedly punctured for prothrombin-time and coagulation-time tests hardly constitute optimum management during this early critical period. In most instances any treatment deemed necessary can be initiated in the patient's home. Removal to a hospital can be accomplished, if indicated, when this critical period has passed.

Anticoagulants in Old Age.—It has been repeatedly claimed that old age provides special indication for the use of anticoagulants in acute coronary occlusion. Wright[12A] considers that, although the incidence of thromboembolism may be no greater in aged than in young patients, the older patient is more vulnerable and less likely to survive the consequences of thromboembolism. We have shown, however, that no justification exists for the concept that age is an important factor in determining the prognosis in the individual case.[13] Statistically, there is a higher incidence of serious attacks among older patients and consequently a higher incidence of thromboembolism. For this reason alone anticoagulants have shown a greater life-saving action in patients over 60 years old than in younger patients.[1a] It has not been recognized, however, that the prognosis for a severe attack or a mild one is uninfluenced by age. Our comparisons of cases of similar severity in different age groups have repeatedly demonstrated similar mortality figures.[2] One must therefore conclude that the initial clinical appearance of the patient, irrespective of age, constitutes the best index to his future course and the deciding factor regarding the need for anticoagulants.

When the patients with mild cases who are treated at home by conservative measures and the persons with serious attacks who manifest specific contraindications to anticoagulant therapy are taken into account, probably less than half of all the cases can be considered suitable for anticoagulant therapy. This low estimate should not detract, however, from the value of anticoagulants in properly selected patients—those with poor prognostic signs—since the administration of anticoagulants in such cases constitutes a major advance in the treatment of acute myocardial infarction.

Summary and Conclusions

From all available evidence, it appears that anticoagulant therapy is neither necessary nor desirable for the large segment of patients who sustain their first attack of acute myocardial infarction and present no unfavorable criteria for recovery at the time of the first examination. An analysis of 1,000 good-risk cases has shown an over-all mortality rate of only 3.5% and an incidence of fatal thromboembolism appreciably less than 1%. In 511 of the 1,000 cases, careful scrutiny throughout the period of hospitalization to discover evidence of thromboembolic phenomena disclosed the presence of these complications in only 3.7%. All of these episodes, moreover, were of a mild nature, and not a single instance of cerebral or peripheral arterial embolism was encountered. In the entire series of 1,000 patients, embolism to the brain occurred in one case while embolism to an extremity was not observed. Inasmuch as hemorrhagic complications from anticoagulant therapy may equal or exceed any benefits theoretically possible in this low-risk group, such treatment is unwarranted for good-risk cases.

Although less than half of all patients require anticoagulant therapy, this low figure should not detract from the established value of such treatment in poor-risk cases. The age of the patient has no bearing on immediate prognosis in the individual case and should not be considered an important factor indicating or contraindicating the use of anticoagulants in acute myocardial infarction. Prognostic classification at the onset of an attack affords a practical and reliable means of selecting patients for anticoagulant therapy in acute coronary occlusion. The clinician's knowledge of the life history of this disease has progressed sufficiently in recent years to warrant the individual selection of cases for anticoagulant therapy.

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Drs. Howard B. Sprague, Virgil Dorset, Alexander A. Doerner, Charles F. Naegele, and La Vere G. White assisted in this study.

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Mental Health and Civil Defense.—Maintaining the mental health, developing morale, preventing personality breakdowns, or providing for the treatment of psychological casualties is a major field of civil defense practice. All civil defense personnel will need to know the elements of psychological first aid and the plans for dealing with the psychologically sick. In addition, it is important for many civil defense workers to find a greater appreciation of the influence that the quality of their leadership, their educational procedures, and their own interpersonal relations have upon the stability and readiness of their colleagues in the face of acute stress.—W. G. Hollister, Some Mental Health Aspects of Civil Defense for Public Health Workers, *American Journal of Public Health and the Nation's Health*, October, 1956.

DRUGS OTHER THAN ANTICOAGULANTS IN TREATMENT OF ARTERIOSCLEROTIC HEART DISEASE

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• *Atherogenesis can be pictured as a process in which an inherited defect of arterial structure permits the development of atherosclerotic plaques under the influence of secondary factors such as hypertension, renal disease, and certain hormone imbalances. Drugs that alter the concentration of the blood lipids and lipoproteins have been studied as to their influence on this process; none of those tried by the authors, including sitosterol, have given convincing results. Data from three representative patients during periods longer than two years showed that normal variations of blood cholesterol values exceeded the changes attributable to sitosterol and that observations over shorter periods must give misleading results. A plan for the diagnosis and therapy of familial hyperlipemia is described, and in about 75% of the patients with this condition it has been controlled by a fat-free breakfast, a fat-free lunch, and no restriction on fat at the evening meal. The treatment of atherosclerosis, however, remains unsettled except that the patient's weight must be controlled and that secondary aggravating causes must be diligently searched for.*

While investigation in the field of anticoagulants has advanced to the point where at least two divergent views can be expressed in the same journal without mayhem, this is not the case with the subject of the treatment of arteriosclerotic heart disease with drugs other than anticoagulants. My co-workers and I do not subscribe to the Duguid theory of the origin of coronary atherosclerosis.[1] At the risk of oversimplification, I have attempted to show diagrammatically the process of atherogenesis as I believe it is generally accepted, with a few remaining controversial points, in the United States (fig. 1). It is postulated that there is an inherent defect at the junction of the intima and media of the coronary artery, and I believe that this defect is an inherited characteristic. It is probable that this defect would eventually cause atherosclerotic plaques to develop, but there are also many secondary factors that undoubtedly speed up the process. Among these are hypertension, renal disease, myxedema, hypothyroidism, diabetes, hyperlipemia, hypercholesteremia, and a disturbance in the balance of the sex hormones in the body. Each of these secondary factors has been reported in conjunction with an increased incidence of atherosclerosis. When atherosclerosis occurs in the very young, one or more secondary factors can usually be demonstrated. Thus, it is of extreme importance in the prevention of atherosclerosis or in the delay of its progress to use what standard therapy we have available now or may have in the future to combat these secondary factors.

The first lesion that is seen experimentally is usually one that appears to be inflammatory at the junction of the intima and media. A collection of lipid material is seen next. At first, this material closely resembles in composition the circulating lipids of the blood. As this lipid infiltration becomes older the composition changes, and there is relatively more cholesterol and less of the other lipids present. If this infiltration progresses, it will become a "yellow" or "lipid" plaque, and its age, rather than the rapidity of its growth, is probably the determining factor in its composition. As the lipid plaque ages, scarring and calcification may take place, and it then becomes what is termed by Dr. Russell L. Holman a "pearly plaque." The lipid plaque is reversible in the experimental animal while the pearly plaque is not, and we have reason to think that this is also true in humans.[2] Certainly, from a histological viewpoint, it would be difficult to see how the pearly plaque could be reversible.

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At this point I have discussed atherosclerosis as it can occur in the body without any clinical indication of its presence. Only when complications occur are we able to recognize clinically that atherosclerosis is present. These complications may be of several varieties, such as hemorrhage into the base of the

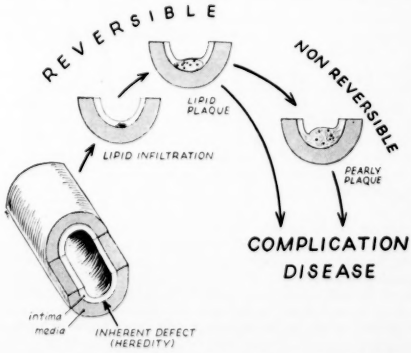

Fig. 1.—Diagrammatic illustration of the origin of atherosclerosis.

plaque, clot formation on the plaque, and narrowing of the lumen by the space occupied by the plaque. These result in an inadequate blood supply to the tissue distal to the plaque; the symptoms and signs of

this inadequacy we call disease. It is conceivable that a lipid plaque may be of sufficient size to cause angina pectoris and still be reversible with subsequent relief of symptoms. It is also quite conceivable that complications may cause recognizable disease as a result of a pearly plaque that has been present for years without either growth or regression.

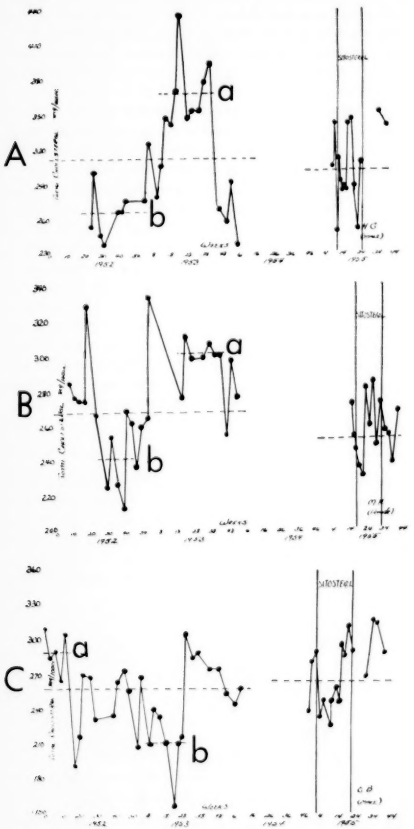

Fig. 2.—Fluctuations in blood cholesterol levels of three patients during a two-year control period (*left*) and a 20-week period of administration of sitosterol (*right*). Broken lines represent the mean cholesterol levels. It should be noted that these have been exaggerated by the scale used in the coordinates since cholesterol values are shown starting at the lowest recorded levels.

Treatment of Atherosclerosis

In accordance with this concept of the genesis of atherosclerosis, it seems logical that the ideal approach to the treatment of atherosclerosis should be in the early detection and reversal of atherogenesis. The treatment of the patient with irreversible atherosclerosis will have to be symptomatic. Since treatments for many of the secondary factors mentioned above are separate subjects in themselves, I shall discuss only those drugs that have been used to alter the concentration of the blood lipids and lipoproteins.[3]

I have tried without success, at one time or another, almost all the wide variety of drugs that have been reported to have had a desirable effect. Early attempts were made to lower the blood cholesterol level and more recently to change the ratio of the alpha to beta lipoprotein. It is important here to point out that hypercholesteremia may be either primary or secondary, and it may be secondary to a variety of conditions. The hypercholesteremia of myxedema, for instance, can usually be controlled easily by the use of dessicated thyroid.

At the Post-Graduate Medical School of New York University, our efforts to lower the blood cholesterol level have been directed toward the effect of drugs on essential familial hypercholesteremia as well as normocholesteremia. The drugs we have tried have included dessicated egg plant, lecithin, choline bitartrate, methionine, inositol, and several preparations of the vegetable phytosterols, including sitosterol and stigmasterol. Of the latter we have concentrated for the most part on the sitosterols. All of these drugs except the sitosterols can, I believe, be dismissed without much controversy as ineffective.

Sitosterols.—At the present time, there is a true difference of opinion as to the value of the sitosterols. Several reports of their effectiveness have appeared.[4] We, however, have used a number of different preparations of sitosterol and have found none of them to be effective.[5] We feel that the difference of opinion as to the usefulness of sitosterol is due to several causes. One, undoubtedly, is in the selection of patients whose secondary hypercholesteremia might be corrected by recognized therapy for the primary disease. We have also excluded from our studies patients with familial hyperlipemia; these I will discuss in detail later.

This selection of patients is not the only cause for disagreement as to the efficacy of this material. We have observed in our patients, during control periods of two years and longer, that there may be an extremely wide variation in their blood cholesterol levels. This is particularly true if the level of the cholesterol is high and may be true in patients that have survived a myocardial infarction (fig. 2). Here we have a control period of just over two years and a period of drug administration of 20 weeks. If one compares the mean cholesterol level of the entire control period to that of the period of drug administration, there is little obvious difference in graph C while there appears to be some difference in graphs A and B. However, if the period of sitosterol administration is compared to a 20-week portion (a) of the control period, the mean of the cholesterol level recorded during the period of drug administration is much lower than the mean recorded during the selected control period. If, however, we choose another 20-week period (b) of the control period, we can show an equally dramatic ele-

vation of the cholesterol level during the administration of sitosterol. Thus, the findings depend upon the selected comparison, rather than on the efficacy of the drug in treatment.

It is our contention that when results are ascribed to therapy they must be clearly beyond natural variations determined over a long period of time. Dr. Donald Mainland, chairman of the department of medical statistics at New York University College of Medicine, agrees with us in this opinion and further states that such data do not lend themselves to statistical analysis.

Estrogens.—It has been recognized for some time that women appear to have some protection against the clinical manifestations of atherosclerosis until the menopause, when this protection disappears. It has also been recognized that myxedema, diabetes, and certain other conditions wipe out this protection. Barr and his co-workers [6] pointed out in 1951 that the ratio of the alpha and beta lipoproteins appeared to be the one common factor in the protective mechanism. In the alpha-beta lipoprotein profile of a young girl, the alpha peak is higher than the beta peak. In the unprotected young male, the alpha peak is characteristically lower than the beta peak, and in some males there is little if any demonstrable alpha peak. In Barr's report, he pointed out that many of the conditions that seemed to wipe out the premenopausal protection of the female are accompanied by the male type of lipoprotein pattern in the female.

Horlick and Katz [7] demonstrated that young cockerels could be protected from atherosclerosis if they were given enough estrogen to wipe out their secondary male characteristics. Both Barr and Katz [8] have reported the effect of estrogen on survivors of myocardial infarction. Others have shown interest in this approach, but I shall limit my remarks to the reports of these two authorities. Theoretically desirable changes have been effected in the alpha-beta lipoprotein ratio in a high percentage of patients studied to date. To do this, however, it has been necessary to give completely feminizing doses of the estrogen. Neither of these investigators has as yet recommended this procedure as anything but experimental. They make no claims as to whether morbidity or mortality are decreased. Certainly, it is too early to recommend the use of active estrogens as anything but an experimental procedure.

Our approach has been an attempt to detect the potential predisposition to atherosclerotic disease and to prevent or delay its onset by early treatment. We have attempted to find a substance that would be similar to an estrogen but would not have its feminizing characteristics. It is too early to report on our progress other than to say that we are not discouraged.

Familial Hyperlipemia

While the treatment of familial hyperlipemia does not come under the heading of treatment with drugs, it is so simple that I have included it here. It is part of our working hypothesis that familial hyperlipemia, when present as the heterozygous abnormal, is not the rare condition that the homozygous abnormal is recognized to be. We believe that the chief metabolic defect in this condition is the inability of the body to remove the postprandial lipemia from the blood as rapidly as the normally functioning body can. Over a period of years, lipemia increases in step-like increments, and with it there is a secondary hypercholesteremia. It has been our experience that rigid fat restriction for a period of 30 days will reduce the hyperlipemia and secondary hypercholesteremia. By properly spacing fat intake in time, one can prevent the recurrence of this step-like increase in the blood lipid level.[9]

We advise then, that the fasting serum of individuals 25 to 35 years of age be inspected visually. If it shows opalescence, the blood cholesterol level should be determined. If it is elevated, the patient should be placed on the regimen described. In about 75% of those patients with familial hyperlipemia that we have studied to date, the process can be controlled with a fat-free breakfast, a fat-free lunch, and no restriction on fat at the evening meal. This is not a low-fat diet but merely results in the spacing of the fat intake in time so that the postprandial lipemia can return to normal before the next load of ingested fat.

Conclusions

Most of the information we have regarding the treatment of atherosclerosis is still highly experimental, and much of it is controversial. At the present state of our knowledge, a positive approach can be achieved by the control of the patient's weight and the diligent search for the secondary aggravating causes and a vigorous control of them. One always hopes that newer and better methods of therapy will evolve and that eventually we will have a logical therapeutic approach for each of the many facets of this complicated metabolic condition.

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ALLERGENICITY OF TRANQUILIZING DRUGS

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and
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• *Meprobamate, an effective tranquilizer with low toxicity and a wide range of usefulness, has given rise to allergic reactions in eight patients observed by the authors and in seven other patients reported to the authors by personal communication. The reactions included urticaria, temperature elevation to 40 C, arthralgia, purpura, and, in a woman being treated for lupus erythematosus, a flurry of new skin lesions. Several of the patients with these reactions had previously used mephenesin; physicians might ponder the possibility that mephenesin may presensitize patients to meprobamate, though this has not been established beyond speculation. Reserpine and chlorpromazine have also caused side-effects essentially different and more variable in type. Percentage-wise, the incidence of allergic reactions to the tranquilizing drugs has been extremely low, but the hazard must be kept in mind because some of the symptoms, especially the fever, may confuse the picture during the course of a usual, well-understood clinical entity or syndrome.*

Allergy to drugs is not new. Many of the mechanisms involved have been lucidly set forth in a recent monograph by Alexander.[1] In the past few years, a host of medicaments have been brought out with the semantically inoffensive appellation of tranquilizing, or ataraxic, drugs. These compounds allegedly calm the tense and harassed patient, bringing about a mood change described by Fabing as detached serenity. The effect is less depressing (and descriptively more acceptable) than that of the earlier so-called sedative drugs of the barbiturate and bromide eras. Among those so classified by science writers and drug houses are reserpine (Serpasil), promazine hydrochloride (Sparine), mephobarbital (Mebaral), acetylcarbromal (Sedamyl), glutethemide (Doriden), butabarbital sodium and reserpine (Butiserpine), butabarbital sodium and belladonna (Butibel), pentobarbital calcium and reserpine (Nembu-Serpin Filmtab), ethinamate (Valmid), methyprylon (Noludar), Dimethylane (2-2 diisopropyl-4-methanol-1, 3 dioxolane), hydroxyzine (Atarax) hydrochloride, chlorpromazine (Thorazine) hydrochloride, and meprobamate (Miltown and Equanil).

Many of these drugs have been in use for some time, and their properties, virtues, and defects are generally well known. The newest series are those derived from Rauwolfia serpentina: reserpine (Serpasil and Reserpoid) and Rauwolfia (Raudixin and Rau-Sed); those of the phenothiazine group: promazine hydrochloride and chlorpromazine hydrochloride; and the mephenesin-carbamate chemical linkages designed to relax both nerve and muscle tensions: mephenesin carbamate (Tolseram) and meprobamate (see figure).

Hydroxyzine hydrochloride, a still newer tranquilizer, has had good advance reports and no record of sensitization to it has been reported to date. Barbiturates and other sedatives are said to depress the brain as a whole and to produce some reduction in mental alertness. The ataraxic drugs act on the subcortical area, the midbrain, and the diencephalon, achieving a tranquilizing effect without cortical depression.

Neither the space allotted nor the scope of this presentation will permit a detailed discussion of each of these drugs. We felt, however, in view of the colossal demand and consumption of these medicaments, that it would not be untimely to point out the dangers of sensitization from their use and to report some of our own observations, supplemented by the reports of others, on meprobamate.

We have not observed or received reports of any allergic response to Dimethylane. Occasional annoying regurgitation has been described, but nothing within the limited reference of this paper has come to our attention.

Reserpine

True sensitivity to reserpine is apparently rare, and thus far no reports of such sensitization are recorded in the literature.[2] The following side-effects of a histamine-like nature would account for many of the phenomena observed in connection with its use as a hypotensive agent as well as a tranquilizer.

Skin Eruptions.—Rashes have been reported that, on closer investigation, have proved to be flushes associated with dilatation of the cutaneous or subcutaneous blood vessels.

Read in the Session on Allergy before the Section on Miscellaneous Topics at the 105th Annual Meeting of the American Medical Association, Chicago, June 14, 1956.

Urticaria.—Urticaria has developed in only a dozen or so of thousands of patients. It disappeared when therapy was stopped and recurred on subsequent administration of a tranquilizer. Most of these patients were skin-tested with reserpine itself and the various excipients in the tablet. Only one positive reaction occurred when reserpine solution was administered subcutaneously, and it, too, could have been a histamine-like local response.

Nasal Stuffiness or Congestion.—Nasal stuffiness or congestion appears in varying degree and disappears spontaneously. It is often relieved by topical application of a vasoconstrictor or of an antihistaminic; occasionally these are combined in a single tablet with the tranquilizer.

Malaise.—Aches and pains in the legs are not infrequently experienced after therapy with this drug. These, like certain depressive states induced by the drug, are occasionally seen as concomitants of allergic reactions. This would not necessarily indicate that the two reactions were identical and hence allergic. The cause of this odd leg-pain reaction is not known.

General.—It is of interest that during preclinical trials rather marked skin sensitivity developed in guinea pigs, but no systemic sensitivity was observed in any of the laboratory animals.[2] If parenterally administered injections of reserpine continue to be used in increasing frequency, it is not unlikely that we shall see skin eruptions in human subjects and, perhaps, as a contact dermatitis in the nursing personnel preparing the material for administration. Obviously, precautions against this are indicated.

Chlorpromazine

Considering the estimated more than 8 million patients who have received chlorpromazine since May, 1954, the incidence of complications and sensitizations is extremely low. These seem to appear only after the patient has received the drug for a week or more and seldom occur after six weeks of therapy. No side-effects are specifically associated with long-term use, and it is unusual for a new side-effect to develop after six weeks, unless the dose is raised abruptly. With the exception of jaundice and agranulocytosis, side-effects may often be eliminated by reducing the dose. If these more serious reactions should arise, the therapy should of course be discontinued. There were seven major groups of side-effects to chlorpromazine.

Nasal Stuffiness.—Nasal stuffiness is a minor annoyance and a common accompaniment of chlorpromazine therapy. The cause is not clear, since the drug has minor antispasmodic, anticholinergic, antihistaminic, and adrenolytic activity. Its central action on the nervous system is selectively depressant at the subcortical levels.

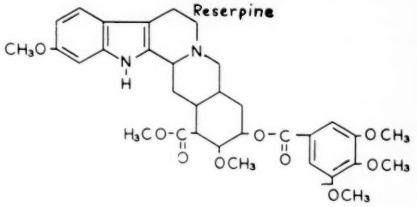
Dermatitis.—A maculopapular, erythematous, pruritic eruption may involve the trunk and extremities, sparing the face, mucous membranes, palms, and soles. It may be generalized or local, involving the anus or genitals. The incidence is probably much lower than 7.5% to 14% reported in some small series, particularly when one considers the many thousands of unreported individuals receiving the drug. In general chlorpromazine therapy could be continued, or resumed, without further dermatitis. This dermatitis must be differentiated from the contact dermatitis that has appeared in some individuals who handle the drug constantly, such as those working with the powder or nurses who prepare frequent hypodermic injections from ampuls.[3]

Photosensitivity.—A rash resembling intense sunburn has been observed after exposure to sunlight. This occurs often enough to warrant interdiction of sunbaths for those patients taking chlorpromazine.

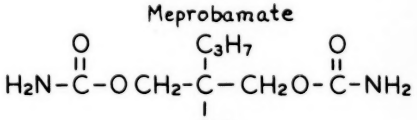
Pruritus.—Itching has occurred in as high as 4% of cases in a small series, without other skin manifestation. In some the therapy was continued without further complaint.

Influenza-like Syndrome.—In another small series the incidence of the influenza-like syndrome, with fever and malaise, reached as high as 16%. This proportion is unquestionably high in relation to the actual number of patients receiving the drug.

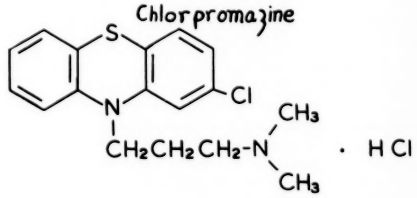
Reserpine



Meprobamate



Chlorpromazine



Agranulocytosis.—Agranulocytosis is fortunately of low incidence, probably less than 0.3%. It occurs within 20 to 60 days of therapy, occurs more often in females, and may begin with little notice, even when routine blood cell counts are being done. One must be on the lookout for sore throat, stomatitis, or other signs of infection. Administration of antibiotics and corticotropin (ACTH) is standard therapy. Hypoplastic anemia is occasionally encountered. At times a transfusion is advisable.

Jaundice.—After less than one week of chlorpromazine therapy, few, if any, patients develop liver complications. After the first week, from 0.8% (or less) to 1.4% of patients may show jaundice. The true nature

of the pathological process is not known. It may be due to allergy or idiosyncrasy. There is bile stasis, with little or no inflammation. When present the white blood cells are lymphocytic, though in rare cases the presence of eosinophils has been striking.[4] Presence of eosinophils in the peripheral blood may serve as a useful point by which differential diagnosis between "chlorpromazine jaundice" and true obstructive jaundice can be made. Fever and mild influenza-like symptoms may be the presenting complaints and may be accompanied by pruritus. Itching may not appear, however, until icterus develops. In general, the therapy should be stopped, though in several instances it has been reinstituted without recurrence of jaundice. The duration of the jaundice may be shortened by administration of corticotropin or cortisone. The immediate as well as the long-term prognosis is good.

Miscellaneous.—Laryngeal edema has recently been described by Brill[5] as an allergic manifestation to chlorpromazine therapy. In the case reported, the condition of the patient became critical and the patient required hospitalization.

Meprobamate

Meprobamate is the newest of the widely used ataraxic drugs. It combines the pharmacological action of mephenesin with that of carbamic acid, to function as an interneuronal blocking agent. It has tranquilizing and muscle-relaxant effects and is said to have some anticonvulsant properties. Its early recognition as an effective tranquilizer in a wide range of clinical tension states and its low toxicity led to immediate acceptance. So great has been the demand for this drug since mid-1955 that there have been appreciable lengths of time when it was not obtainable. Surveys have estimated that 2 million or more prescriptions per month have been written for it. The appearance of allergic reaction was noted in 3 of 187 cases by Selling.[6] We have eight cases of our own to add to this number as well as seven others reported to us by personal communication. Given below are the major groups of side-effects.

Urticaria, Angioneurotic Edema.—Urticaria and angioneurotic edema with local and generalized swellings occurred, with rather marked erythema. The skin became generally warm or actually hot, especially when there was fever. This complication arose within the first day or two of therapy or occasionally after a week. In two cases the drug could be given again without untoward effects, but this was not usually the case.

Fever.—Temperatures from 102 to 104 F (38.9 to 40.0 C) were not unusual when fever was observed, and it generally accompanied skin manifestations, usually erythema, edema, and urticaria. One such instance occurred along with a widely spaced papular lesion on the back. It was preceded by a hardly noticeable erythema at the anterior hairline of the scalp four days before, but this had disappeared spontaneously.

Joint Manifestations.—Arthralgias occurred in about one-third of the cases of angioneurotic edema, but one case of fever was notable in that there was swelling and exquisite tenderness in the shoulder joint unilaterally. This patient experienced the same thing once again on reinstitution of therapy. The joint involved had been the site of pain and slight swelling on occasions prior to meprobamate therapy, but no causal or connected relationship between the earlier episodes and these could be established, save perhaps on a "shock organ" basis.

Blood Changes.—Thomas G. Johnston of Little Rock, Ark.,[7] has reported two cases of thrombocytopenic purpura ostensibly after meprobamate therapy in females about 45 years of age. Reports of four cases of nonthrombocytopenic purpura, including a case of one of us (S. D. K.), appeared in a letter in a recent issue of THE JOURNAL.[8] We have found no blood or urine changes in our patients with the other types of allergic reactions.

Cardiovascular Disturbances.—Dr. T. R. Collins of Orlando, Fla.,[9] has observed one patient, a 56-year-old male, who developed erythema and angioneurotic edema with fever and had an irregular rapid pulse. The electrocardiogram revealed small QRS complexes, with a flutter-fibrillation-type rhythm and ectopic ventricular beats.

Miscellaneous.—One of our own patients, a 47-year-old female, under treatment for lupus erythematosus, developed a flurry of new lesions after a few doses of meprobamate. These cleared and were accompanied by no definite changes other than in the skin. Once again "shock organ response" was suggested in the type of reaction observed in this individual. The fogginess of mind and difficulty of locomotion she experienced may have been connected with the drug reaction. Dr. Berger[10] has had reported to him a few instances of bronchospasm in those cases where fever and angioneurotic edema were more severe. Liver and renal involvement were not observed by him or by us.

In our experience in an allergically weighted group of patients there has been apparently a higher incidence of meprobamate sensitivity than for the population as a whole. Skin tests by the scratch method with meprobamate, gelatin, starch, magnesium stearate, and alginic acid (the constituents of the tablets) yielded negative results in all cases. This was not surprising but was attempted in order to determine whether the drug or some other factor was responsible for the allergic reaction.

Comment

In the presentation of the foregoing material no attempt was made to evaluate the various tranquilizing drugs as to their clinical effectiveness. Similarly, treatment of the allergic symptoms arising from these compounds was hardly touched upon other than to suggest immediate withdrawal of the drug. These matters are beyond the scope of this paper and are amply covered in many other publications and reports. We have, however, considered the theoretical possibility of prior administration of mephenesin as a presensitizer for meprobamate. Several of our patients had received this drug at an earlier date. It would appear advisable, then, to alert the profession to the complications, if not the genuine hazard, of sensitization, so that it will be looked for and not confused with, or mistaken for, some other disease process. A sudden rise of temperature during convalescence from an infectious disease or from surgery can present a formidable problem until

its true nature is elucidated. For these reasons it seems timely to call attention to this complication of "tranquilotherapy," especially with the newest of these tranquilizers, meprobamate, which has skyrocketed to such a prominent place in everyday office and institutional treatment.

Hypersensitivity reactions to new drugs should be reported as promptly as possible, so that the patterns of reactions are made generally known to the profession. Once recognized, they serve as guides to rational therapy or aid in the general evaluation of the compound. With the best of laboratory controls and techniques and the many fine efforts they make, the pharmaceutical companies cannot always foresee or forestall the unusual reaction to new products.

Reactions, Allergic or Otherwise, to Tranquilizing Drugs

Reserpine	Chlorpromazine	Meprobamate
Skin rash?	Nasal stuffiness	Angioneurotic edema
Urticaria	Dermatitis, (also contact type)	Urticaria
Nasal stuffiness	Photo sensitivity	Erythema
Malaise	Pruritus	Fever
Leg-ache	Influenza-like syndrome	Arthralgia
Depression	Agranulocytosis	Purpura
Skin sensitivity (experimental animals)	Jaundice	Thrombocytopenic
	Laryngeal edema	Nonthrombocytopenic
		Bronchospasm (rare)
		Cardiac Arrhythmias

Summary and Conclusions

The large number of so-called tranquilizing or ataraxic drugs now at the physician's disposal have produced reactions that are thought to be due to allergic sensitization. It is quite possible that some of the reactions are coincidental. It is possible that prior use of mephenesin might play a role in presensitization. It is obvious that there is some relationship between the number and type of users of these drugs and the incidence of sensitization. Percentage-wise this incidence is extremely low. The untoward effects of many of them are already fully known, and with more time and further use one can anticipate more such instances.

Allergic reactions of the patient, as well as of those who prepare the drugs in manufacture or for therapeutic administration, must be considered, looked for, and, if possible, prevented by proper precautions. The possibility that allergic or drug fever might becloud the issue in the clinical course of a patient under treatment must be borne in mind to avoid unnecessary or erroneous therapy.

The respect and usefulness that any drug commands depend upon what it can do to help the specific patient of the individual doctor. To the conscientious physician, any untoward side-effect becomes an immediate personal problem rather than a distant, well-documented statistic. It is for these reasons that the profession should be promptly informed of any unusual reactions to a drug as observed by physicians who use it in every phase of clinical practice.

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Work After Cardiovascular Disabilities.—The question of optimum duration of disability following various cardiovascular disorders has been discussed. Studies available in the literature and a brief survey of 318 cases occurring in the Manufacturing Operations and the New York Office of the Esso Standard Oil Company during 1955 were reviewed. . . . Certain arbitrary statements about average length of disability can be made with full knowledge of their limitations as applied to the individual case: 1. Coronary insufficiency will usually result in three to four weeks absence. 2. Myocardial infarction will cause from 12 to 16 weeks disability. 3. Congestive heart failure irrespective of its etiology, usually means four to six weeks absence. 4. Cerebral vascular disease produces between two and six months absence. 5. Symptomatic essential hypertension without major cerebral, cardiac or renal involvement produces on the average from two to five weeks disability. 6. Thrombophlebitis will result in three to four weeks absence. 7. Varicose veins treated medically will average about a week of absence. Where surgery is undertaken four weeks will usually be lost from work. 8. Severe peripheral arteriosclerosis was not a common cause for absence in our experience. Where it is, the absence will be measured in months and return to full duty unlikely. In conclusion, evaluation of a person with cardiovascular disability for return to work is a highly individual matter. Average figures . . . can be given.—J. J. Thorpe, M.D., The Optimum Time for Return to Work Following Various Major Cardiovascular Disabilities, *Industrial Medicine and Surgery*, July, 1956.

ROLE OF TRANQUILIZING DRUGS IN ALLERGY

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• *Many allergic patients fail to respond to the usual type of allergy management, and in most of these cases there is a large psychogenic component that must be treated before clinical improvement can be expected. Tranquilizing drugs provide available therapy to block certain interneuronal pathways adversely affected by anxiety and tension. The treatment of allergies can yield better results and longer-lasting successes by utilizing the "total" or combined type of treatment that embraces both the physical and the emotional factors involved. However, the tranquilizers should be used only as an adjunct to the therapy of allergy where there are certain states of anxiety and tension, and not as a replacement of accepted diagnostic and curative procedures.*

An allergic individual may suffer the consequences of life's psychological stress and strain like anyone else and may, from time to time, require additional aid to allay this threat to his feeling of well-being.

In accordance with modern medical concepts, it is advisable to treat the whole patient, his sick emotions as well as his diseased organs. Indeed, the physician may be called upon to deal with a particular home, school, or job situation in which the patient may find himself. Until such time as we are better informed and trained in this newer approach, it is well to use modern chemical modes of therapy to block certain interneuronal pathways adversely affected by anxiety and tension. Needless to say, those patients requiring specialized care should be referred to a competent psychiatrist to deal with the psychogenic factors involved. However, the allergist should learn to deal with the emotional problems of his patient. This he can do, provided he develops a helpful, understanding attitude and is willing to listen patiently.

Recent studies have shown the importance of psychogenic factors and personality disorders in allergic disease.[1] Psychotherapy alone, however, does not produce as good results as does management of the specific allergy, in which the offending agents are identified and eliminated or treatments for desensitization are administered. Experience teaches us that even better results and longer-lasting success are obtained by the "total" or combined type of treatment, which embraces both the physical and the emotional factors involved.

Ever since man first appeared on the horizon there has been a never-ending search for that magic potion to soothe his aching body and troubled soul. Small wonder, then, that substances like opium, fermented spirits, and analgesics have enjoyed such extensive usage and popularity. However, one cannot help but feel that nature has purposely thwarted our attempts to attain a state of tranquility through drugs or other artificial means by imposing serious penalties for partaking of her "forbidden fruit," namely, unpleasant side-reactions, increasing tolerance, habituation, and physical and mental deterioration.

The modern tranquilizers to be considered (chlorpromazine [Thorazine],[2] reserpine [Serpasil],[3] and meprobamate [Miltown and Equanil] [4]) have for the most part none of the above undesirable features, except for a few minor side-effects. However, they should be used with caution, for this modern modality can lull us into a state of false security. A happy, sedated, tranquil patient may not heed the warning signs of disease and thereby delay important diagnosis and treatment. This is comparable to the situation sometimes encountered with penicillin, corticotropin (ACTH), cortisone, and other "wonder drugs," in which spreading infectious processes may become masked and cause the death of the patient. Tranquilizing drugs should, therefore, be used as adjuncts only, to allay certain states such as anxiety and tension and not as a replacement of accepted diagnostic and curative procedures.

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Read in the Session on Allergy before the Section on Miscellaneous Topics at the 105th Annual Meeting of the American Medical Association, Chicago, June 14, 1956.

Material and Methods

Clinical observations were made on three groups of allergic patients receiving chlorpromazine, reserpine, or meprobamate. Patients who exhibited undue anxiety, mental depression, or tension were selected for study, together with those individuals whose symptoms failed to respond to the usual types of allergy management. The nature of the drugs used was unknown to the subjects, who were merely told to "use this."

Chlorpromazine.—Chlorpromazine [2] was introduced into the United States in May, 1954, after extensive use in Europe. It was first synthesized in France in 1951. Clinically, it has been useful in widely divergent conditions involving soma and stress reactions, such as nervous and mental disturbances, nausea and vomiting, motion sickness, alcoholism, Parkinsonism, drug addiction, pruritus, pain, obstetric difficulty, hiccups, fear of surgery, tuberculosis, asthma, neurodermatitis, headache, and arthritis. Toxic effects range from minor reactions such as drowsiness, tachycardia, dryness of the mouth, dizziness, nasal congestion, constipation, pupillary changes, increased appetite, and urticaria to more serious side-effects such as postural hypotension, chills and fever, shock, jaundice, leukopenia, and agranulocytosis.[5] Because of its potentiating effects on sedatives, narcotics, and anticonvulsants, chlorproma-

zine should be used cautiously in cases in which the former have been administered. It is contraindicated in patients with arteriosclerosis and cardiac disease and in the weakened and debilitated patient, in whom a significant drop in blood pressure could prove disastrous.

Chlorpromazine was given to 59 patients (37 adults and 22 children) who ranged in age from 18 months to 72 years (table 1). Dosage averaged 40 mg. daily for children up to 5 years, 75 to 100 mg. for older children, and 100 to 150 mg. for adults. All of the patients with urticaria received, initially, two injections of 25 mg. each of chlorpromazine on the first and second days of treatment. The medicament otherwise was given orally, as outlined above, for a period of from two to six weeks.

Table 1 shows the response of this group to chlorpromazine therapy. Of the 59 patients studied, 19 (32.2%) were benefited by the drug. Improvement was based on subjective as well as objective findings. While no patient was "cured," those helped were able to tolerate the remaining symptoms, required less supplemental medication, rested better at night, and showed much less evidence of their disease such as wheezing and dermatitis. All of the eight children with asthma had exhibited various degrees of personality disorders, mostly extreme restlessness, frequent nightmares, and nonconforming type of behavior. Chlorpromazine, through its calming action, enabled these youngsters to sleep better at night, with less notable wheeze and cough. Incident to this improvement in both behavior and allergic symptoms (children became more tractable) was a distinct improvement in the parent-child relationship. A tired, anxious parent, awakened night after night by the child's incessant coughing and wheezing, is in no condition to satisfy the emotional needs of the offspring. Four patients, two children and two adults, had to discontinue the therapy because of marked weakness and sleepiness. No case of jaundice or blood dyscrasia occurred in this series.

TABLE 1.—*Response of Allergic Patients to Chlorpromazine (Thorazine)*

Diagnosis	Cases, No.	Improved	Unimproved	% Improved	Side-effects
Urticaria and angioneurotic edema	12	3	9	25	Stuffy nose, 1; drowsiness, 2
Neurodermatitis	10	2	8	20	Drowsiness, 2; weakness, 1
Asthma					
Children	8	4	4	50	None 0
Adults	15	5	10	33	Drowsiness, 3; tachycardia, 2
Eczema, children	14	6	8	43	Drowsiness, 2
Total	59	19	39	32	13 (22%)

Reserpine.—Rauwolfia serpentina,[4] the ancient Indian drug, has been used in the United States since 1950 in cases of hypertension and chronic heart disease, thyrotoxicosis, and various neuropsychiatric conditions. The alkaloid fraction, reserpine, has received quite a reputation for its tranquilizing effect, as well as for its ability to reduce the mean arterial blood pressure and the pulse rate. These reactions may not become apparent for several days after start of treatment (lag effect), and the action tends to persist for as long as two to six weeks after the therapy is stopped. Gaunt [3d] feels that this substance stimulated adrenocortical activity. Toxic reactions [3e] are generally of a benign nature, namely, drowsiness, nasal congestion, fatigue, heavy feeling in the lower extremities, diarrhea, sighing respirations, and increase in gastric acidity.

Reserpine therapy was tried in 52 patients (34 adults 25 to 75 years of age and 18 children 2 to 14 years of age) (table 2). Dosage ranged from 1 to 4 mg. daily for adults, and 0.4 to 1 mg. for the younger age group, administered in divided doses. The medication was continued for from two to six weeks. In those instances in which the drug produced favorable results, repeated courses still are being given. Eleven of the 52 patients, or 21%, were improved after therapy with reserpine (table 2), benefit being judged by statements from the patients, amelioration of symptoms, and the quantity of supplemental medication required for relief. The five children helped by the drug evidenced relaxation of the tension and restlessness that were prominent prior to this type of therapy. This may have contributed to the improvement in their allergic symptoms by reducing the tendency of reflex coughing and itching. Reserpine therapy did not aid patients with asthma, hay fever, gastrointestinal disorders, or eczema although, admittedly, the number of cases in all categories were insufficient for proper evaluation of the medicament's effectiveness in allergic diseases.

TABLE 2.—*Response of Allergic Patients to Reserpine (Serpasil)*

Diagnosis	Cases, No.		Improved		Unimproved		% Improved	Side-effects
	Adults	Children	Adults	Children	Adults	Children		
Asthma	9	8	1	2	8	6	18	Fatigue, 2 adults
Eczema	2	6	0	1	2	5	12.5	None
Hay fever	10	1	2	0	8	1	18	Drowsy, 2 adults and 1 child
Gastrointestinal allergy	...	1	..	0	...	1	...	Abdominal pain, 1
Urticaria and angioneurotic edema	7	2	2	1	5	1	33.3	None
Headache (allergic)	6	...	2	...	4	...	33.3	Stuffy nose, 1; drowsy, 1
Total	34	18	7	4	27	14	21	8 (15.4%)
	(52)		(11)		(41)			

Only one patient had to discontinue the treatment because of adverse reaction—aggravation of colic and diarrhea in the case of the gastrointestinal allergy.

Meprobamate.—Meprobamate [4] was introduced to the medical profession early in 1955 as Miltown and Equanil. It had been synthesized five years earlier by Ludwig and Piech.[6] According to Berger [7] who de-

scribed the pharmacology of meprobamate, the drug has a selective action on interneurons, is a good anticonvulsant, and produces relaxation of skeletal muscles, without affecting respiration, the heart, or any other vital organ. It has few toxic effects and acts as a mild sedative, with drowsiness and headache being listed most frequently as side-reactions. In the light of its diverse reactions on the body and effectiveness in anxiety and tension states, the drug is thought to have a selective action on the thalamus. Miltown, mephenesin (Myanesin),[8] and Equanil were administered to 83 adult patients over a six-week period as follows: (1) Miltown, 1 tablet (400 mg.) four times daily for two weeks; (2) mephenesin, 1 tablet (500 mg.) four times daily for the next two weeks; and (3) Equanil, 1 tablet (400 mg.) four times daily for the final two weeks. These patients were selected because of complaints in excess of the degree warranted by the physical findings, persistence of symptoms despite the usual allergy management, or complaints of an emotional nature, i. e., undue anxiety, tension, or mental depression.

Comment

Tranquilizing drugs can serve a useful purpose in treatment of allergic individuals to relieve certain psychiatric states that tend to aggravate the physical manifestations of their disease. While no patients were "cured" in this study, many were made more comfortable, appeared to tolerate their symptoms better, and showed a lessening of signs such as wheezing and skin eruptions. These drugs will not replace specific therapy of allergic diseases, nor can they substitute for the valuable drugs that are often lifesaving to the asthmatic patient, such as epinephrine, corticosteroids and other hormones, aminophylline, and fluids given orally and parenterally. As reported by Moyer and co-workers[2c] chlorpromazine can be highly effective in cases of status asthmaticus. Caution must attend its use here, however, lest an already sedated, weakened patient be relaxed into a deepening sleep from which he never recovers. I know of one such case. We must not neglect to institute measures for the correction of pathophysiological mechanisms that threaten the life

TABLE 3.—*Miltown, Mephenesin, and Equanil in Allergic Patients*

Diagnosis	Miltown			Mephenesin*			Equanil			Side-effects†
	Patients, No.	Improved No.	Improved %	Patients, No.	Improved No.	Improved %	Patients, No.	Improved No.	Improved %	
Asthma	34	14	41	33	4	12	34	12	35	Urticaria, 1; drowsy, 3
Headache (allergic)	6	3	50	6	1	16.6	6	3	50	Headache and dizzy, 1
Hay fever	19	8	42	18	3	16	19	9	47	Headache and colic, 1; drowsy, 3
Eczema	10	2	20	10	0	0	10	0	0	Urticaria, edema, ache, and fever, 1
Gastrointestinal allergy	2	1	50	2	0	0	2	1	50	None
Urticaria and angioneurotic edema	12	4	33.3	9	0	0	11	3	25.4	Erythema and edema, 1; drowsy, 3
Total	83	32	38.5	78	8	10	82	28	34	14 (17%)

* Used in lieu of control placebos.

† Side-effects noted were in patients receiving Miltown and Equanil.

While none of these patients recovered completely from the allergic conditions, 32, or 38.5%, definitely improved when receiving Miltown (table 3).

Most of the individuals helped by meprobamate therapy have continued taking the drug from time to time as the need for a tranquilizer has become necessary. In fact, several, who were able to identify the drug, hoarded part of the tablets against future need, just in case their pharmacy "ran out." Patients remarked about the favorable relaxing and sedative effects of meprobamate, its ability to relieve anxiety and tension, and the absence of dopiness the next morning. No signs of addiction occurred, nor did anyone complain of a "let-down" feeling when the therapy was discontinued.

Six patients had to stop therapy because of extreme drowsiness (one case), dizziness and headache (one case), and erythematous eruption with urticaria and angioneurotic edema of face and neck (four cases). The patient with marked somnolence fell asleep in a customer's house while making a delivery. The rest of the patients were able to continue with the medication, despite mild headache and dizziness, which gradually wore off as time went on. Urine and blood studies showed no abnormalities in the patients studied, other than the adverse reactions listed.

On occasion, a combination of two or more tranquilizing agents may produce the desired effect where no benefit obtains with just one. A case in point is a 63-year-old woman hospitalized recently because of status asthmaticus. This patient failed to respond to therapy with aminophylline or epinephrine, which only stimulated her and made her extremely restless and panicky. Therapy with meprobamate and the barbiturates proved worthless, failing to calm her. Then, an injection of 15 mg. of chlorpromazine was given intramuscularly, with a remarkable relaxing effect in about 15 minutes, enabling the attending physician to begin intravenous administration of badly needed fluids to correct a severe degree of dehydration. Penicillin for residual pneumonitis after a "virus" infection, and potassium iodide drops for the expectorant action, helped this patient make a prompt recovery. Her state of relaxation was maintained by orally given chlorpromazine, 10 mg., plus 1 tablet (400 mg.) of meprobamate, given three times daily.

To illustrate an important use of meprobamate, brief mention may be made of another case, a 35-year-old female school teacher, with a four-year history of

generalized eczema and neurodermatitis and marked sensitivity to feathers, house dust, wheat, and egg-white. Avoidance of these factors as much as possible and desensitization therapy produced moderate relief, but she still slept poorly and itched considerably at times. Despite a show of tears at almost every visit, this individual maintained: "I've read where allergies can be triggered by the emotions, but mine can't be! I never worry, have a happy home life, wonderful husband, and most of the things I need." Quite obviously she was depressed, tense, and anxious. Therapy with chlorpromazine and reserpine was tried, with no favorable result. Therapy with meprobamate, however, sedated and calmed her, and she itched less and slept better. During the second week of such therapy she was no longer depressed, and, for the first time, she brought out into the open a problem concerning the second of her two children, a severely handicapped, mentally retarded, spastic, 4-year-old girl, whom she had been forced to place in a state institution. After several interview sessions, during which she unburdened herself of long-hidden guilt feelings concerning this child, the dermatological condition became much improved.

Allergists are certainly aware of the many patients who fail to respond to the usual type of allergy management. Most of these individuals are usually found to have a large psychogenic component that must be treated before clinical improvement can be expected. We can prevent these patients from falling into the hands of various disreputable treatment centers that abide in certain sections of the United States by learning how to help the patient gain insight into and face his emotional problems. Otherwise, we become but another "symptom" to the patient as he traverses deeper into the depths of his psychosomatic illness.

Summary and Conclusions

In a preliminary study, tranquilizing drugs were found to be of therapeutic value in allaying tension and anxiety states in patients suffering from various allergic conditions. The sedative and relaxing effects seemed to produce a "secondary gain" in reducing the intensity of the allergic symptoms in a certain number of cases. Presumably, these drugs act on the hypothalamus or thalamus, or their action is mediated through some other psychophysiological mechanism. This type of medication should be used as a temporary aid only, not as a replacement for accepted modes of therapy, such as identification and treatment directed against the offending agents plus correction of complicating factors like infection, dehydration, and circulatory disturbances. In keeping with modern medical precepts, physicians working in allergy should consider the patient as a whole, deal with the psychogenic factors involved, as well as the physical manifestations, and help the individuals concerned develop insight regarding the impact of their emotions on the allergic state.

Chlorpromazine (Thorazine) was of some benefit to 19, or 32.2%, of 59 patients suffering from various allergic conditions; meprobamate (Equanil and Miltown) helped approximately 37% of 83 cases; reserpine (Serpasil), the alkaloid fraction of Rauwolfia serpentina, brought improvement to 11, or 21%, of 52 patients studied; and mephenesin (Myanesin), used in lieu of control placebos in the meprobamate series, benefited about 10%. These results warrant further study of the effect of tranquilizing drugs in allergic diseases.

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The meprobamate used in this study was supplied as Miltown by Wallace Laboratories, New Brunswick, N. J., and as Equanil by Wyeth Laboratories, Philadelphia. The chlorpromazine used in this study was supplied as Thorazine by Smith, Kline & French Laboratories, Philadelphia.

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CLINICAL NOTES

POSTMORTEM CESAREAN SECTION WITH SURVIVAL OF INFANT

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There has been a certain degree of apathy regarding the performance of postmortem cesarean section for at least two reasons: 1. It is rarely successful. 2. It is usually a sad experience for both the attending physician and the surviving family. In addition, certain legal, moral, and religious considerations may deter rather than encourage the procedure.

Only 113 successful postmortem sections have been reported in the world literature of the last 250 years.[1] This represents a small percentage of the total number attempted. For example, the Minnesota maternal mortality study [2] reveals that only 14 postmortem sections were attempted in this state from 1950 to 1954, and none of the infants survived. Despite these statistics, we believe that if the fetus is of viable age it should not be left in utero at the time of the mother's death. If it is, the only possible mortality rate is 100%. If it is removed by cesarean section, it has some chance of surviving and doing well. The mortality rate must therefore be reduced.

It is our purpose to show by means of an illustrative case that mere statistics should not discourage one from attempting this procedure, despite the most trying circumstances.

Report of a Case

At 1:30 a. m. on May 13, 1956, one of us was called by the wife of our obstetrician, who was off duty and unavailable at the moment. She gave the phone number of a home where a woman was gravely ill and needed immediate help. The patient's husband proved to be in a hysterical state and hung up in the middle of a very brief telephone conversation. At the residence, five minutes later, the woman was found to be deeply cyanotic and without respirations. The ambulance crew, already present, were fruitlessly attempting to administer oxygen by mask. The patient was large, obese, grossly edematous, and obviously near term. Slightly sanguinous, frothy material was slowly exuding from her nose and mouth. There was no radial pulse, and auscultation at the cardiac apex revealed no audible heart sounds. At the moment that the absence of an apex impulse was discovered, simultaneous palpation of the abdomen revealed vigorous fetal movements.

Owing to the husband's hysterical state and to the lack of resuscitating apparatus, it was decided not to attempt delivery by cesarean section in the home. Instead, our two surgeons were contacted, and they made preparations at the hospital for our arrival. Loading the patient into the ambulance was slow because of her bulk (her weight was 350 lb. [158.7 kg.]), the lifeless flopping of her arms over the sides of the stretcher, and the narrow doorways. However, with remarkable speed she was carried to the ambulance, transported to the hospital, unloaded, and carried by stretcher through a narrow, angular hallway into the ground floor of the hospital. A cesarean section was done immediately, with the patient still on the stretcher; there was no visible active bleeding. A normal full-term male infant was extracted with ease, and oxygen was immediately administered by resuscitating apparatus at about 30 to 40 cycles per minute. The infant's heart tones were strong and regular from birth on, and his skin became pink within about one minute of the initiation of resuscitation. Crying and adequate spontaneous respirations began within about three minutes.

It was assumed that the mother's death occurred almost simultaneously with the physician's arrival at the house at 1:35 a. m. Subsequent reenactment of the events described above confirmed our estimates of the time elapsed between the death of the mother and the administration of oxygen to the baby. The events included examining the patient, alerting the surgeon by telephone, loading the patient onto the stretcher and into the ambulance, backing the ambulance through a darkened driveway, the 12-block ride to the hospital, unloading the patient and maneuvering through the basement, and the 10-second cesarean operation. The total time was 11½ minutes.

History and Present Illness of Mother.—The mother was 44 years old, gravida 4 para 3, with children aged 18, 7, and 3½ years. Despite the pleas of her husband, she had refused both prenatal and postpartum office care during her last two pregnancies. In fact, she had no record at the clinic whatsoever, and our meager information was obtained from her husband and from the hospital record of her confinement in September, 1952. At that time she had preeclampsia, with a history of edema and headaches, a blood pressure at the time of admission of 194/120 mm. Hg, and albuminuria.

According to her husband, the patient's expected date of confinement was late May, 1956. She had had swelling of the legs for about a month. One week before her death she had an attack of severe headache and scotomas. There was steady weight gain of unknown amount. Suddenly, during the night, about an hour before death, she developed severe dyspnea and orthopnea and then collapsed and became comatose at about the time we spoke to the husband by telephone. The patient did not complain of headache or of chest pain during the final episode. She had no convulsions.

Postmortem Findings.—About 14 hours post mortem an autopsy was performed by one of us, (H. DeK.) with Dr. William Hunt, obstetrician and gynecologist of the Park Region Medical Center in Fergus Falls. Permission for examination of the cranial cavity was not obtained. The findings were as follows: The body was large and obese, with much of the weight, estimated at 350 lb., attributable to anasarca. Lividity was marked in the face and neck. Bloody fluid exuded from both nostrils. All the body cavities contained substantial amounts of pale yellow fluid. The heart was normal in size, and the myocardium, valves, and coronary arteries all appeared normal. Owing to the adiposity of the omentum and mesentery, to the ascites, and to the enlargement of the uterus, the domes of the diaphragm were displaced high in the chest, leaving very little room for pulmonary expansion. Both lungs were markedly edematous, and on cut section the dependent portions were full of the same type of pink frothy transudate that had welled up into the nasal passages at the time of death. The liver was slightly enlarged and pale yellow in color. The kidneys were normal in size, and on section their cortices appeared to be devoid of visible glomeruli. The left adrenal gland appeared normal grossly; the right adrenal gland was not found. The uterus was enlarged, and there was no evidence of dilatation of the cervix. The placenta had been discarded.

The microscopic examinations, done by Dr. James S. McCartney of the University of Minnesota, were reported on as follows: "Sections of the kidneys show lesions of eclampsia. It required special stains to be sure whether this was eclampsia or

From the Fergus Falls Clinic.

glomerulonephritis. The lungs show edema and congestion. The adrenal shows a small cortical adenoma. The liver shows a marked degree of fatty metamorphosis."

Subsequent Progress of Infant.—As noted above, this infant had a strong apex beat at birth, his color was good, and he was crying within three minutes of delivery. His respirations were moderately labored and of a grunting nature. Slight external stimulus resulted in a generalized clonic reaction and marked carpal spasm. Therefore, an umbilical vein was isolated, polyethylene tubing was introduced, and 5 cc. of calcium gluconate was given intravenously, followed by 100 mg. of ascorbic acid (vitamin C) and 10 cc. of lactated Ringer's injection. The tubing was anchored and remained patent for the next six days.

The infant was also given crystalline penicillin and vitamin K. However, in spite of the fact that he was doing better than anticipated, generalized twitching persisted. The nurses noted that he perspired profusely and became cyanotic at times. When he was about 53 hours old the infant had a generalized convulsion and became markedly cyanotic. The cyanosis cleared slowly, but he remained semicomatose. About three hours later he was given 3 cc. of calcium gluconate, 100 mg. of ascorbic acid, and 2.5 mg. of vitamin K through the inlying polyethylene tube. During this procedure extreme respiratory embarrassment occurred, and he became markedly cyanotic and appeared moribund. Oxygen was administered by mask, and artificial respiration was begun. In less than a minute the color improved, the infant's cry appeared to be more lusty, and respirations were easier.

This last episode marked the crisis, apparently, in the infant's struggle to survive. From this time on he took formula well. He would twitch occasionally, and tended to lie with his left leg drawn up onto the abdomen, but the leg could be passively extended with ease. This was the only sign that pointed to any localized central nervous system damage, and it gradually disappeared. Reflexes were essentially normal.

The baby's birth weight was 7 lb., 1.5 oz. (3,218 gm.). On his discharge from the hospital, when he was 34 days of age, he weighed 9 lb., 1.5 oz. (4,125 gm.). At the age of 4 months he was seen by Dr. Lyle French of the University of Minnesota Hospitals for neurological evaluation. The only positive finding was a head circumference 4 cm. greater than average at this age. However, the child has continued to progress in a normal fashion. He contracted pertussis from a sister who had not been immunized. This cleared with tetracycline therapy.

At the time of writing there are discernible none of the neurological stigmas that one might expect to follow the rugged events of the child's entrance into the world. Such abnormalities—should they appear in later years—might even follow a so-called normal birth. At any rate, we must say that he is progressing quite normally. Indeed, the child's development has compared favorably with that of his siblings.

Comment

The question will naturally arise whether the woman was dead at the moment of the doctor's arrival at the home. It is our belief that she was dead because of (*a*) the extremely deep, blue-black cyanosis; (*b*) the absence of respiratory excursions of the thorax; (*c*) the absence of any visible to-and-fro bubbling of the froth covering the nose and mouth but merely a slow steady out-welling of this froth, characteristic in death from pulmonary edema; (*d*) the absence of radial pulse; and (*e*) the absence of an audible apex beat on stethoscopic auscultation. These findings are sufficient for the pronouncement of death and, short of opening the chest and observing the heart, constitute final evidence. From this moment, 11½ minutes elapsed before delivery of the fetus at the hospital.

As for the fetus, what insults to its internal metabolism had occurred to make its survival up to the time of delivery highly improbable? In the first place, the mother had had toxemia for a month and now had acute preeclampsia. It is well known that toxemia per se raises the fetal mortality rate. Second, the mother had been in severe pulmonary edema that resulted in death in an hour. Gas exchange in the lungs is greatly retarded under these circumstances. Oxygenation of the maternal hemoglobin is further reduced by acidosis and accumulation of carbon dioxide.[3] These factors cooperated to reduce the oxygenation of the fetal circulation before the mother's death.

All these insults, added to the time elapsed between the mother's death and the delivery of the baby, make the baby's survival a noteworthy event. These observations, together with the satisfactory progress of the baby, suggest a revision of our thinking on the resistance of the fetal brain to damage from prolonged anoxia.

Summary and Conclusions

An infant, delivered by cesarean section at the hospital 11½ minutes after its mother's death at home from eclampsia and pulmonary edema, survived and has progressed normally to the time of writing. This outcome should encourage efforts on the part of physicians to save the lives of unborn infants after their mothers' death from any cause, no matter how rugged the conditions.

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Closed Head Injury.—It has been shown that a closed, apparently uncomplicated head injury may be followed by a diffuse degeneration of the white matter and consequently may completely and permanently incapacitate the patient. The extreme dementia produced by such a lesion should not be confused with coma, which has different physical signs. The nerve fibre degeneration is not due to cortical cell loss, nor to infarction or laceration of brain substance. Its pathogenesis has not been determined but evidence points to physical damage of nerve fibres at the time of injury as a likely cause. It is at present not possible to say how frequently such white matter degeneration occurs because it has not been looked for in acute head injuries. In our series of 26 patients dying from head injuries six weeks or more after the accident, it was the significant pathological finding in about one-third of the cases.—S. J. Strich, Diffuse Degeneration of the Cerebral White Matter in Severe Dementia Following Head Injury, *Journal of Neurology, Neurosurgery and Psychiatry*, August, 1956.

MEGALOBLASTIC ANEMIA DURING PRIMIDONE (MYSOLINE) THERAPY

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In the past two years, 15 cases of megaloblastic anemia occurring in patients undergoing anticonvulsant treatment with either diphenylhydantoin (Dilantin) sodium or primidone (Mysoline) have been described in the British literature. A patient presenting a similar syndrome came under our care in 1954.

Report of a Case

A 48-year-old single woman, complaining of fits, was first seen in the clinic of the New York Hospital-Cornell University Medical Center in 1940. Examination revealed partial hemiparesis of the right side with associated muscle atrophy and flexion deformities of the limbs. The tentative diagnosis established was that of idiopathic epilepsy (grand mal and petit mal) and hemiparesis secondary to a birth injury. Therapy with phenobarbital was instituted and there was some diminution in the intensity of the sporadic seizures.

Between 1940 and 1946, the patient received at one time or another various combinations of phenobarbital, sodium bromide, diphenylhydantoin, and trimethadione (Tridione) (table 1). In 1946, the patient required medical attention for mild abdominal pain. Physical examination was unrevealing. A hemoglobin value of 8.1 Gm. per 100 cc. was found. Menses were not excessive, and guaiac test on the feces was negative on the one examination that was done. On gastric analysis, there was no free acid found in the fasting specimen, but 17 degrees of free acid was present 30 minutes after the administration of histamine. Although there were no findings suggestive of pernicious anemia, the patient was given liver extract (Lextron, liver-stomach concentrate with ferric iron and vitamin B complex) orally, while the administration of phenobarbital and trimethadione as anticonvulsant agents was continued. The patient improved symptomatically and refused to have regular blood studies done. The next hemoglobin value, obtained in 1949, was normal.

In 1952, treatment with primidone was instituted. By the end of that year, the patient was receiving 250 mg. five times daily. In January, 1954, the patient noted weakness, lassitude, impairment of her sense of balance, and, rarely, vertigo. These symptoms increased, and sore throat, anorexia, and intermittent burning of the tongue were also noted. When admitted to the hospital, she denied that gastrointestinal bleeding had occurred and stated that her periods were not excessive. She admitted that her dietary habits had not been good and that she had not eaten adequate amounts of meat at times. Physical examination on admission showed normal temperature, pulse rate, respiration rate, and blood pressure level. The patient was pale and had the deformities previously noted. The tongue was papillated but not reddened. The liver was palpated 2 fingerbreadths below the costal margin. The spleen was not enlarged. Neurological examination showed no sensory disturbances. The results of radiologic study of the gastrointestinal tract, including the esophagus, stomach, duodenum, and colon, were within normal limits, except for several small jejunal diverticula. Gastric analysis again showed the presence of free acid after the administration of histamine. Examination of the blood revealed marked anemia with predominant macrocytosis and also microcytosis and some polychromatophilia (table 2). Sternal marrow aspiration disclosed definite megaloblastic changes (see figure). After the discontinuation of the administration of primidone, without any change in the other medication and with no improvement in diet, there was a prompt development of reticulocytosis (16% reticulocytes) and gradual correction of the anemia.

TABLE 1.—*Anticonvulsant Agents Taken by Patient 1940-1956*

Name of Drug	Range of Daily Dosage, Mg.	Period of Administration
Phenobarbital	100-200	1940: 2/3 ... 1951: 11/15 ... 1954: 7/17 ... 1955: 1/5
Diphenylhydantion sodium	200-400	1943: 5/18 ... 1944: 10/10 ... 1948: 4/19 ... 1949: 6/15 ... 1954: 2/31 ... 1956: present
Trimethadione	600	1946: 4/30 ... 1947: 3/23
Methylphenylethylhydantoin	200-400	1949: 6/15 ... 1951: 2/14 ... 5/8 ... 1953: 7/13
Primidone	250-1,250	1951: 12/26 ... 1954: 7/16 ... 12/21 ... 1956: present
Meprobamate	800	1954: 9/25 ... 12/21

In December, 1954, primidone therapy was reinstituted. At that time, blood cell counts were within normal values. The patient again failed to keep appointments. When she finally returned to the hematology clinic in February, 1956, she again complained of weakness and tiring easily. Physical examination revealed essentially the same findings as previously noted. Blood cell counts again demonstrated the presence of a marked macrocytic anemia, with some multilobed polymorphonuclear leukocytes. Megaloblastic changes were again found in the bone marrow. The patient was continued on primidone therapy but received in addition 2.5 mg. of folic acid daily. With the patient on this regimen, the anemia was completely corrected in four weeks. Remission has continued with the patient on therapy with primidone and folic acid.

Comment

Of the previously reported instances of megaloblastic anemia associated with the administration of anticonvulsant agents, 12 cases occurred in patients taking diphenylhydantoin usually prescribed with phenobarbital.[1] One patient who had been treated with a combination of diphenylhydantoin, phenobarbital, and methylphenylethylhydantoin (3-methyl-5, phenylethylhydantoin [Mesantoin]) without developing anemia presented a megaloblastic anemia two months after the institution of primidone therapy.[2] One patient who

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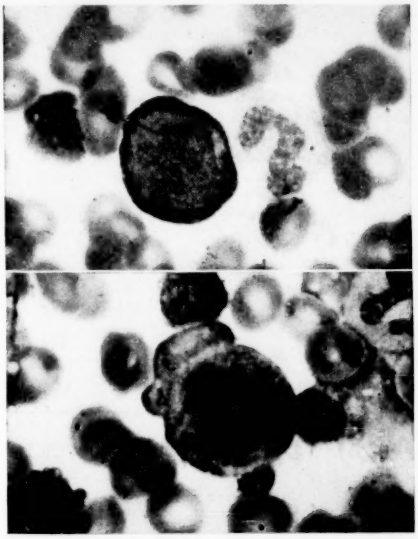
developed a megaloblastic anemia while taking primidone and phenobarbital was described by Girdwood and Lenman.[3] Two cases in which the development of megaloblastic anemia followed the administration of primidone alone were reported recently by Fuld and Moorehouse.[4] The present case appears to be the fifth reported instance of megaloblastic changes following the administration of primidone and is the first case in the United States to be described.

Most patients who developed a megaloblastic anemia while taking anticonvulsant medicaments responded to therapy with folic acid, although occasionally the administration of cyanocobalamin (vitamin B_{12}) in very large doses was also successful.[5] Studies in some of the reported cases indicate that the megaloblastic anemia occurs in spite of the presence of normal levels of cyanocobalamin in the serum and normal absorption of cyanocobalamin [2] and evidence of normal absorption of folic acid.[4] One patient, treated with diphenylhydantoin, possibly had an abnormal balance of fat in the feces,[1c] although, in the other patients in whom studies on fecal fat were performed, fat absorption appeared to be unimpaired. The original response of our patient to the discontinuation of the administration of primidone alone, without the addition of folic acid, suggests that this drug, by itself, can in some manner induce a megaloblastic change in the marrow.

Theoretically, megaloblastic anemia may be produced by deficiency of cyanocobalamin, folic acid, or ascorbic acid, either from dietary deficiency, failure of absorption, or, possibly, by abnormal metabolism. The studies made in the case reported above suggest that neither malabsorption of cyanocobalamin or folic acid nor dietary deficiency played a major role. In an attempt to demonstrate interference of the utilization of cyanocobalamin or folic acid by primidone in a biological system, Chanarin of the department of pathology (hematology), Postgraduate Medical School of London, introduced serial dilutions of primidone (maximum concentration, 2 mg. per 100 cc.) into



Photomicrographs of sternal marrow aspiration, demonstrating megaloblastic changes.

assays of cyanocobalamin and folic acid by microbiological methods (Euglena gracilis and Streptococcus faecalis R.). No evidence of interference with the utilization of either cyanocobalamin or folic acid by

TABLE 2.—*Hematological Data in Relationship to Primidone Therapy*

Date	Hemoglobin, Gm./100 Cc.	Red Blood Cell Count, Thousands	Hematocrit, %	MCV,* Cubic Microns	MCH,† Micro-micrograms	MCHC,‡ %	Reticulocytes, %	Description of Red Blood Cells
11/29/46	8.1	2.8	...	...	...	...	1.1	Poikilocytosis
2/10/49	14.1	4.7	...	...	...	...	...	
6/29/49	14.2	5.5	...	...	...	...	...	Poikilocytosis and stippling
12/26/51			Primidone Therapy Started					
7/14/54	8.0	2.5	21	140	53	38	—	Macrocytosis
7/16/54			Primidone Therapy Discontinued					
7/20/54	9.5	2.5	27	108	38	35	—	
7/24/54	11.0	2.8	32	114	39	34	16.0	
7/28/54	...	...	...	...	...	...	5.0	
8/17/54	11.8	3.0	...	...	...	...	...	Anisocytosis and poikilocytosis
9/21/54	15.7	3.8	...	...	..	...	...	
11/16/54	12.8	4.2	...	...	...	...	...	
12/ 2/54	13.9	4.1	40	98	34	35	...	Slight macrocytosis
12/21/54			Primidone Therapy Started					
1/ 3/55	13.2	3.9	41	105	34	32	...	
3/15/55	13.1	3.7	38	103	36	35	...	
5/17/55	11.7	3.6	36	100	33	33	...	
6/13/55	12.0	3.5	...	...	...	...	...	
2/21/56	11.1	2.9	33	114	38	34	...	
3/20/56	11.3	3.0	30	100	38	38	2.4	Slight macrocytosis and multilobed polymorphonuclear leukocytes
3/20/56			Folic Acid Therapy Started: Primidone Therapy Continued					
4/24/56	13.0	4.0	43	103	33	30	...	

* MCV=Mean corpuscular volume (normal: 80-94 cubic microns).
† MCH=Mean corpuscular hemoglobin level (normal: 27-32 micromicrograms).
‡ MCHC=Mean corpuscular hemoglobin concentration (normal: 33-38%).

these organisms was demonstrated. The mechanism of the megaloblastic change produced by the administration of primidone remains unexplained, although the more favorable clinical response of these patients to the administration of folic acid than to that of cyanocobalamin suggests some derangement in vivo of the metabolism of folic acid by the action of the drug.

Summary

A patient developed megaloblastic anemia in association with anticonvulsant therapy with primidone. The anemia responded to withdrawal of primidone without the institution of other therapy or a change in diet and recurred one year after the reinstitution of primidone therapy. Treatment with folic acid, without the withdrawal of primidone, then resulted in a second remission of the anemia.

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Dr. D. L. Mollin of the Postgraduate Medical School of London gave advice in the preparation of this report.

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5. Footnote 1 *a* and *d*.

COUNCIL ON FOODS AND NUTRITION

The Council has authorized publication of the following commentary.

PHILIP L. WHITE, SC.D., *Secretary.*

WHO TREATS ARTHRITIS?

From time to time books on medical matters are written for the laity, particularly for those suffering from one disease or another. This procedure has much to commend it when the books are written by competent and reliable authorities on the subject and in such a manner that they may lead to improvement in an individual's health rather than to its detriment.

Unfortunately, other less critical or less informed individuals frequently write books that contain considerable misinformation, which in certain instances actually may be harmful to some patients. Worse than this, many books advocate self-treating rather than consulting and relying upon the advice and counsel of a physician. An example of a book not written in the best interest of the public is one by Dan D. Alexander, Ph.D., entitled "Arthritis and Common Sense." It was first printed in 1951 and has now gone through more than 10 printings, rating high on the New York *Times* nonfiction popularity list.

The book is intended, as the author states, "mainly for the person with little or no medical knowledge . . . to give a clear explanation of his affliction." The thesis is that "arthritis is a deficiency of specific dietary oils . . ." resulting ". . . in a lack of steroid hormones and a lack of better lubricating oils for the joints." The book has a foreword by a physician who, of course, is entitled to his opinion concerning the treatment of arthritis. It is not our purpose here to assess the treatment recommended but merely to comment upon the body of the book.

The misinformation throughout the book is characterized by such statements as: "Speaking of weight, one cup of black coffee with an oily meal has more fattening power than a glass of milk. The coffee turns against the oils in your food, and increases the energy potential of the meal." Many people who read this book will not know that since black coffee contains no calories it cannot affect the caloric value of the meal.

Of interest to the physician is the author's description of a physical examination:

> In too many cases, a person with arthritis has never had a *complete* physical examination. You may doubt that statement, and say that you have often been examined from head to toe at your doctor's office. True, but what questions were you asked? Did anyone take a record of your past diet? Did the subject of cod liver oil come up in the discussion? Were tests made to determine the oil content of your body and of the foods you had been eating recently? . . . we shall now give you a guide on how to obtain a *complete* physical examination the next time you visit your doctor.

The following five pages did just this, plus the diagnosis and treatment for the symptoms that the physician might find. For instance:

> Is there an itching near the lower spine? If so, this is an early warning in many cases that your spinal vertebrae are going to have future trouble. It is quite possible that the oils near the lower vertebrae are drying out. You are alerted by this sign that in five or ten years you may expect serious back ailments to set in.

Statements such as these may sound too ridiculous to be considered seriously when there are so many urgent matters to occupy the physician's attention. Arthritis is an urgent matter, however, and approximately 550,000 people who are either sufferers of arthritis or fear that they will be have purchased the book. Those "with little or no medical knowledge" are not considering these statements ridiculous!

The Federal Trade Commission has charged that the course of treatment recommended in the book is not, as advertised by the publishers, an adequate treatment or cure for all kinds of arthritis and rheumatism. The deception of the public by this advertising, the complaint concludes, violates the FTC Act. At best, the author and the publisher can be forced to change their advertising.

Physicians would do well to peruse this book. They may be asked by their patients whether the diets contained therein are safe and whether they will cure arthritis. Cod liver oil may have a place in the treatment of arthritis, but only as a part of a planned therapeutic regimen carefully worked out by a physician who possesses knowledge of the facts.

There are those individuals who do not ask their physician's advice. They may very possibly be in the majority, indicating an even more important reason for the physician to be aware of this type of literature. Is it not one of his responsibilities to his community and to his profession to exert all of the influence he can in combating food and health misinformation whenever and wherever it may occur?

COMMITTEE ON COSMETICS

Report to the Committee

The following paper was presented at the symposium, "The Rational Use of Cosmetics in Medical Practice," in Chicago, June 13, 1956. This symposium was sponsored by the Committee on Cosmetics in cooperation with the Section on Dermatology at the 105th Annual Meeting of the American Medical Association. This is the second in a series of papers, the first of which appeared in THE JOURNAL, *March 2, page 740.*

VERONICA LUCEY CONLEY, *Secretary.*

CUTANEOUS EFFECTS OF SOAPS AND SYNTHETIC DETERGENTS

Raymond R. Suskind, M.D., Cincinnati

In modern history, the development and widespread availability of hygienic methods, such as the use of cleansing agents or detergents and water, has significantly enhanced both social and economic progress. During the 20th century, the consumption of soap rose markedly so that by the year 1935 about 2.6 billion pounds were sold in the United States.[1] Prior to World War II, synthetic detergents for household use made their debut, and with them a new era in personal and household hygiene began. For the housewife their introduction made possible more efficient washing of clothes, dishes, and interior surfaces. For persons whose skin could not tolerate the use of soaps, mild effective synthetics were a fortunate substitute. In 1954 the total soap and detergent consumption soared to an estimated 4.5 billion pounds. In that year it was also estimated that over 75% of the packaged household detergents were of the synthetic type.

Effects on Normal and Abnormal Skin

Cutaneous cleansing agents, no matter what their chemical configuration, can be classed as cosmetics since they are employed to maintain the health and normal function of the skin. The field of their application is the common meeting ground of the physician, nurse, industrial hygienist, and soap and cosmetic manufacturer. Their widespread use for personal hygiene and household and industrial cleansing has resulted in important cosmetic as well as other health benefits. Their employment under diversified conditions has also made it necessary for the physician to attempt to understand their normal as well as abnormal effects on human skin.

The salutary effects of soaps and synthetic detergents on normal skin include the removal of cellular debris, desquamating keratin, cutaneous secretions, pathogenic micro-organisms, air pollutants, and a variety of common contactants indigenous to our culture, among them the potentially hazardous substances found in industry. Soaps and synthetic detergents are effective preventive and/or therapeutic agents in a large group of dermatoses, such as acneform eruptions, seborrhea and seborrheic dermatitis, pyodermas, infestations, dermatoses associated with hyperkeratoses, e. g., callosities, keratosis follicularis, follicular keratoses, and even psoriasis. In such instances, detergents and water not only cleanse the skin but remove or alter the consequences of the pathological activity, and, in some instances, discourage the growth of and remove the causative agents, such as horny plugs, keratinous accretions, crusts, scales, accumulation of secretions, bacteria, fungi, and arthropods.

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Mode of Action

The mode of action of any detergent, including soap, is very complex and not completely understood. Its surface activity is manifested in a variety of ways, which are described as (1) lowering of surface tension, (2) reduction of interfacial tension, (3) increase in wetting power, (4) emulsification, and (5) deflocculation. Detergents differ considerably in the degree to which they can effect all of these things. The molecules of both soaps and synthetic detergents are characterized by a water-soluble portion and another segment, usually a long hydrocarbon chain, which is soluble in oils and their solvents. Because of this unsymmetrical configuration, the detergent molecules have a tendency to concentrate in the surface of aqueous solutions, thereby lowering the surface tension.[2]

According to Kooyman and Halberstadt,[2] the washing process includes the following mechanisms:

1. The detergent, on dissolving, lowers the surface tension of the water. This permits more intimate contact between the water and the material to be cleansed (fabric, skin, or other material) and enables the solution to penetrate between the material and the particles of soil.

2. The solution emulsifies and to some extent dissolves any grease or oil that may be present.

3. Insoluble particles of dirt are wetted, surrounded, and held in suspension by the detergent solution.

4. Mechanical action aids in loosening the soil from the surface to be cleaned.

5. The solution and the suds or lather, containing emulsified or dissolved oil and grease and suspended dirt, are rinsed away.

Lane and Blank [3] believe that the endogenous and exogenous components of skin soil are to some degree water-soluble but are mostly oily and solid materials. In the removal of such components, emulsification occurs, and the oil-skin interface is replaced by two new interfaces: skin-detergent and oil-detergent interfaces. In this fashion the oily soil is emulsified, and the solid particles are suspended in the detergent solution so that they can be removed by rinsing. Other factors may affect the detergent action of a given surface-active agent, including temperature and mechanical factors, such as agitation, friction, and rinsing. Since soaps and synthetic detergents are both surface-active agents, the essential mechanisms of detergency are the same for both groups of materials.

Cutaneous Alterations

Of some concern to the physician is the effect that these materials may have on normal skin and the skin of persons with established dermatoses. Much has been written about "housewives' eczema" and "winter eczema," two rather common cutaneous syndromes in which soaps and synthetic detergents appear to be etiological factors. In this connection, specific alterations in the skin that may be caused by these cleansing agents should be reviewed.

The alkalinity of a soap solution will result in the swelling and softening of the most superficial horny layers of the skin. In "normal" use of soap for cleansing, the swelling or liquefaction of keratin is not significant.[4] The pH of the cutaneous surface material is usually altered temporarily by soap-and-water cleansing, and the normal cutaneous secretions such as sebum are removed by such ablutions. Under ordinary circumstances the skin will tolerate soap-and-water cleansing without visible damage.

The nature of the cutaneous alterations that may accompany cleansing or immersion in solutions of synthetic detergents is not as well understood as the effect of soap. Synthetic detergents will emulsify skin soils effectively and, in the process, remove the oily layer of sebum. It has been reported that no significant differences in surface lipid values can be found during a period in which either a bar soap or an anionic synthetic detergent has been used by older patients.[5] The keratin changes noted in the skin with excessive immersion in soap solutions are not produced by nonalkaline synthetic detergent solutions. They are produced, however, by certain household, synthetic detergent products of relatively high pH comparable to that of soap. It has been demonstrated by Van Scott and Lyon [6] that solutions of certain household soap and synthetic detergent products denature keratin so that sulfhydryl groups are exposed. An experimentally useful property of sulfonated and sulfated anionic detergents was described by Stoughton,[7] who showed that these substances have a selective affinity for the elastica. These biochemical alterations, the sulfhydryl-exposing effect and anionic detergent affinity for elastic fibers, have yet to be correlated with clinical damage. They may be either biochemical manifestations of cutaneous injury or just incidental findings not related to the dermatitis induced by these materials. In any case, further critical examination of these effects may be very revealing.

Pathological Alterations

It is fairly well agreed that, under appropriate circumstances, pathological alterations in the skin can be induced by soaps and synthetic detergents. The clinical manifestations regarded as characteristic of this group include (1) the chronic redness, scaling, and fissuring that resembles chapping, (2) winter dermatitis that occurs on various parts of the body, frequently as superficial nummular patches, at the onset of cool weather, and (3) the acute or chronic dermatitis of the hands in housewives and persons in other work involving frequent immersion of the hands in cleansing agents. Despite some disagreement, there is good evidence that allergic sensitization to commonly used household soap and synthetic detergents is a rare occurrence.[8] The effect of soaps, detergents, and their additives on the water-holding capacity of keratin was recently investigated by Blank and Shappirio.[9] Their effect on water inbibition is of considerable interest, since skin dryness and scaling more frequently result from dehydration than a deficiency of natural oils.[10] These investigators found that the water-holding capacity of keratin was reduced equally by immersion in solutions of soaps and synthetic detergents but was not altered by the addition of sodium triphosphate. If this alteration in keratin is reflected in clinical damage, there appears to be no difference in

the changes induced by either soaps, synthetic detergents, or chemicals commonly used in the formulation of washing products.

Clinical Problems

The clinical problems arising from apparently excessive immersion in soap solutions have been explained on the basis of keratin damage from alkali, the irritant effect of certain fatty acids, the removal of surface

Results of Immersion of Hands in Solutions of Heavy-Duty Synthetic Detergent and "Built" Laundry Soap for Two-Week Period

	No. of Subjects
Test and control hands improved	33
No change in test or control hands	8
Test hand unimproved, control hand improved	1
Test hand improved, control hand unimproved	1
Test hand worse, control hand improved	0
Test and control hand worse in first week but improved in second week	2
Total	45

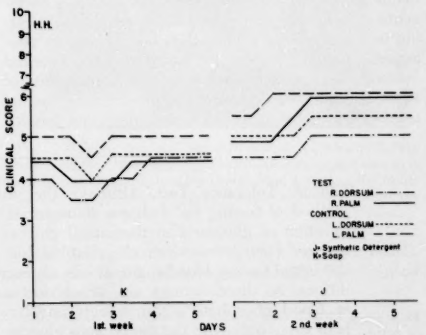
lipid, and the alteration in buffering capacity of the skin. From clinical observation, it is obvious that this is only part of the story. The theory that the dermatitis attributed to the use of household synthetics is exclusively the result of the specific product acting as a primary irritant is also not convincing. It appears that the circumstances that cause soap or detergent dermatitis include the cleansing agent as one of a set of complex factors. Perhaps other influential factors are (1) cold weather, frequently characterized by low relative humidity, (2) other contactants in the kitchen and laundry, such as vegetable, fruit, or meat juices, other foods, and bleaches, and (3) other cleansing and polishing products containing abrasives, excess alkali, or irritating petroleum solvents.

The household use of soaps and synthetic detergents may aggravate a variety of dermatoses, including (1) conditions characterized by dry skin, such as ichthyosis and xerosis of senile skin, (2) atopic dermatitis, (3) irritant or allergic contact dermatoses, (4) infectious eczematoid dermatitis, and (5) tinea pedis and the vesicular ids arising from it. The effects of the potential irritancy of specific products were demonstrated by exposing persons with acute or chronic dermatoses of the hands to commercial soaps and synthetic detergents. These were patients in whom the cleansing agents were suspected to be causative or aggravating factors. The results of single-immersion exposures were reported by Jambor.[11] He observed no significant changes in the dermatitis of the hands in hospitalized subjects when the involved parts were immersed passively in 0.5% aqueous solutions of a variety of products at 41 C (105 F) for one-half hour daily for four days.

His failure to observe changes after the immersion of the hands in a detergent aroused the curiosity of Drs. Morris Meister, Samuel R. Scheen, and myself, and we decided to follow this with a study in which the conditions were more severe.

The duration of exposure was increased to 30 minutes twice daily for two weeks. Two heavy-duty cleansing agents, a laundry detergent with a pH of 10.0 and a "built" laundry soap with a pH of 9.9, were employed in this test. This test was also carried out in hospitalized patients. The right hand, which was used as the test hand, was immersed in a solution of the washing product at 41 C (105 F); the left hand, which was employed as the control, was immersed for the same period of time in tap water (pH 7.7-8.5) of the same temperature. The dorsum and palm of each hand were observed with the aid of a skin microscope, and scoring was made on a numerical basis. Such observations were recorded each morning prior to the first daily immersion and six hours later prior to the second daily immersion. A summary of the results in the first 45 patients studied is presented in the table.

Although aggravation in the dermatitis of the test hand was expected, frank improvement was noted in the large majority of instances in the hand that had been immersed in the synthetic detergent and soap solutions as well as in the control hand that had been immersed in tap water. In most cases, the hands of the subjects responded similarly to immersion in the synthetic detergent or soap as they did to soaking in tap water. Contrary to our expectations, in no instance did immersion in the cleansing agent result in the dermatitis of the test hand becoming worse as compared with the control hand. In two cases dermatitis in the test hand became significantly worse during the first week, but the control hand behaved similarly. Both hands showed notable improvement during the second week of the test. A typical clinical score record is shown in the figure. The subject was a 51-year-old man who had had a severe eczematous dermatitis of all extremities for six months. It was not possible to



Graph showing clinical score of patient with dermatitis of hands after immersion of test hand in 0.5% solution of soap during first week and synthetic detergent during second week as compared with after immersion of control hand in tap water for 30 minutes daily during two-week period.

determine the cause of his skin problem. He was one of 33 subjects whose hands improved on exposure to detergent solution as well as tap water.

It must be emphasized that in this study the subjects were removed from their home or work environments and were allowed to come into contact with

one set of carefully controlled factors. The question arises as to whether this immersion exposure was as severe as that found in the home. If we are concerned with dishwashing exposures, the average concentration of synthetic detergent products employed by the housewife is about 0.3%,[12] equivalent to 0.06% of the actual surface-active agent. Home surveys have estimated that the average housewife who washes dishes by hand spends about 39 minutes per day in this activity.[13] Our exposure factors of a 0.5% concentration for 60 minutes per day were therefore much more severe than those experienced by the average housewife. Universal worsening of the dermatoses was not induced by the immersion. This leads us to believe that the circumstances in which soaps and detergents have been indicted as causing or aggravating dermatoses are much more complex than have been anticipated. The roles of the ambient conditions and attending exposure to other chemical materials found in the household or in comparable work are frequently mentioned but not understood. The improvement observed in most of the patients tested in this series may be attributed either to the anti-inflammatory effect of soaking or to the hospitalization itself, which removes the patient from the milieu responsible for the eruption. The elevated temperature and pH of the test solutions did not appear to interfere measurably with the therapeutic effect of these immersions.

Comment

I should again like to stress the medical, cosmetic, and social importance of soaps and synthetic detergents. There are still very large gaps in our knowledge about the cutaneous effects of these substances. The diagnosis of dermatitis from soaps and synthetic detergents is made frequently, and more cases are appearing in the physician's office than heretofore. An etiological diagnosis cannot be made on circumstantial evidence but rather by a thoroughgoing evaluation of all of the possible exposure and predisposing factors cited in this report. It would seem appropriate, too, for the medical profession and the manufacturer to pool their technical resources and to integrate their research efforts in a systematic and critical investigation of these unsolved problems.

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Glucose Tolerance Test.—Although the oral glucose tolerance test is still the simplest method of testing for diabetes, it measures other variables. By the use of a rapid intravenous injection of glucose a mathematical glucose utilization constant can be calculated. This is quicker (one hour), free of variables due to absorption and independent of the height of the initial fasting blood sugar. It can distinguish between mild diabetes and nondiabetic conditions. Its disadvantages are largely technical such as multiple venipunctures. Further use of blood phosphate measurements ancillary to the glucose tolerance test has indicated that it is of value only with the intravenous glucose tolerance test and cannot be applied to individual cases. A new and valuable approach is that of combining steroid stress with the glucose load. A single dose of cortisone (200 mg.) orally or ACTH (100 mg.) subcutaneously given before the test worsens the oral glucose tolerance test. This has been applied to diabetes detection. In diabetic patients and in many siblings of diabetic persons (over fifty years of age) ACTH worsens the glucose tolerance test, but not in control patients. By this method, persistence of impaired glucose tolerance can be demonstrated in some diabetic patients who are in an apparent remission. A flat glucose tolerance curve occurs in many normal people and has been difficult to explain. By simultaneously performed fluoroscopic x-ray examination of the stomach in 26 such persons it has been shown not to be due to delayed emptying-time. The best explanation at present is decreased speed of absorption. In two thirds of the patients studied glucose tolerance reverted to normal on subsequent repetition.—S. B. Beaser, M.D., Diabetes Mellitus, *The New England Journal of Medicine*, Aug. 2, 1956.

MEDICINE AT WORK

DOUBLE-HATTED DOCTORS ARE REMAKING OUR COMMUNITIES

"Members of the medical profession are a hard insoluble mass in the community; all they do is take—they don't want to put anything back."

Soon after Lewis Haas, general manager of the Phoenix, Ariz., Chamber of Commerce, publicly delivered those scolding words five years ago, citizens 1,300 miles across the nation in Decatur, Ill., were clicking their own tongues about doctors. Held high to public view was a survey report that 60% of Decatur residents felt physicians were not interested in making their community a better place to live. Look at Phoenix and Decatur today.

Mr. Haas is eating his words. Now he is telling anyone who will listen, "The Maricopa County Medical Society is one of the most progressive groups within the community." His verbal sting in 1951 smarted but it smartened too. First the doctors launched an automobile safety belt campaign that put these straps in thousands of autos and as standard equipment in every Arizona highway patrol car (fig. 1). Then they teamed up with the state pharmaceutical association and Lederle Laboratories in waging war on accidental poisoning and in putting out a booklet on home safety. The booklet, "What's the Answer," was so successful that there have been 2 million reprints in this country, India, and Japan. Next, the medical society members opened a 24-hour emergency telephone exchange. Last year they helped establish a retirement home for the aged.

Meanwhile, in Decatur, some people still consider "survey" a dirty word. Physicians there have become community heroes. This fall the last of six new schools will open—much thanks to the Macon County Medical Society's 11th-hour support of a construction bond issue, which was being threatened with defeat at the Decatur polls. The doctors, their wives, and P.T.A. teams saved the day by distributing 5,000 leaflets financed by the medical society. The leaflets simply cited school expansion as necessary to good health, less delinquency, and a better future for local youngsters.

"One of the Best Things. . . ."

Inspired with this success, Decatur physicians later went on to rally public support for a sewer bond issue and for a dam to raise the level of Lake Decatur. All three measures won by wide vote margins, amid such plaudits from the citizens as: "If the medical society recommends it, the bond issue must be essential to the welfare of the city," and "One of the best things that has happened to this community is the revival of the medical society's interest in public affairs."

Is somebody asking: Where is the "traditional" physician decorum? What has happened to the "time-honored" concept that medicine and politics do not mix? How can a doctor tend to good doctoring if he spends his time "meddling" in civic affairs? Why don't these "public servant" M.D.'s stick to their profession's "heritage" and code of ethics regarding involvement in lay affairs? Loaded questions, every one of them.

Ask members of the Omaha–Douglas County Medical Society, Nebraska, how their decorum stood up last fall in a United Community Services Fund drive. To generate enthusiasm they marched into a campaign kickoff dinner meeting clad in football uniforms. They laid aside stethoscopes, reached for clarinets and snare drums, and gave out with rhythmic Dixieland jazz. Four of them, dubbed the "Laryngeal Larks," harmonized as a barber shop quartet. One doctor at the dinner meeting kicked up his heels in a Charleston.

Fig. 1.—These Arizona highway patrolmen are adjusting safety belts that have been installed in all state police cars as a result of a safety campaign led by Dr. Paul Jarrett of the Maricopa County Medical Society, in cooperation with other groups throughout the state.

All those physicians wore decorum on their hearts, and in the hearts of their community. They raised $11,000 for the fund.

Ask Dr. Ben Frees, civic leader and former president of the Los Angeles County Medical Society, if he is mixing medicine with politics—or if they are really one and the same. A civic committee has chosen him their chairman to persuade voters next April 2 to approve elimination of smogging incinerators in favor of improved garbage collections.

Medical Practice Is Broad

Since when is setting a broken arm, removing an appendix, prescribing a drug, or delivering a baby the only kind of medical practice? Before he died several years ago after over 40 years as a physician in Ne-

braska, Morris Nielsen led the way to establishment of milk inspection, a sewage disposal plant, paving projects, and a 16-bed hospital in his community. That is doctoring. He also was city physician, member of the local school board, and member of the chamber of commerce. In between these Many Duties (that's what M.D. meant for him) he managed to run his practice and even deliver 3,500 babies, earning praise as "a godfather to everyone in the community."

And there's that last loaded question about heritage and ethics keeping physicians nicely insulated in their antiseptic offices and hospitals. Doctors in Bronx, N. Y., can laugh at that one without even consulting the American Medical Association's principles of medical ethics (first sentence: "The prime object of the medical profession is to render service to humanity.")

Fig. 2.—Double-hatted doctors

In the Bronx several years ago, members of the county medical society finished their daily professional duties and went out to wage an on-the-scene battle against Pugsley Creek. They surveyed the foul-smelling, rat-infested, garbage-laden, insect-breeding creek in order to help persuade city officials that it should be filled in as a serious health hazard. The doctors succeeded, chalking up another achievement in public service. Other endeavors: smoke abatement, safety programs, vote-and-registration drives, free vitamins for the needy aged, better police and fire protection, improved public transportation, and emergency ambulance service.

Public service has become so synonymous with medical practice in the Bronx that the average citizen does not hesitate to bring civic problems to his family physician. The patient feels he will get not only a sympathetic ear, but effective action as well. Behind this reasoning is a requirement of the Bronx County Medical Society that every member must belong to some civic, fraternal, veteran, service, or other community group. This assures a feel of the public pulse, and a field for concerted action on a wide variety of issues. One committee of the Bronx Chamber of Commerce is made up of over a dozen physicians.

You Cannot Stop a Doctor

Where there is a need of any kind in any community today, you cannot stop a doctor from being a citizen; he may even be wearing the hat of a public servant for longer hours than he wears the cap of his profession. Not long ago physicians of the Baltimore County Medical Association were in the market for artists' berets when, in search of an official emblem, they sponsored a design contest for local high school students. They have a fine emblem now. They also brought honor to the $50 prize winner and to two runners-up. And the doctors have gone a long way toward building good will in the school system while encouraging teen-age artistic talent.

A detailed, up-to-date picture of public service performed by physicians will come into view later this year, after the A. M. A. conducts its fifth biennial survey of some 2,000 constituent county medical society activities. Quiz forms will be sent out in a few weeks. The 1955 survey detected the first broad evidence that most of some 160,000 representative physicians were intensely interested in socioeconomic aspects of medicine. Questionnaire replies placed this "nonmedical" topic high on the agenda of medical society meetings. The survey report noted: "Physicians recognize that many problems of this nature confront the profession."

The study showed that doctors all across the nation are active not only in blood banks, disease control programs, and graduate education, but also in organizing and judging poster and essay contests, sponsoring Little League baseball teams and high school science fairs, and working for better civil defense, slum clearance, public education, fire prevention, human relations, and Boy Scout and Girl Scout activities.

Greatest Rewards

Perhaps the most important concept grasped by these thousands of physicians is that the greatest rewards of civic accomplishment come in working with other groups. The Medical Society of the County of New York is the first to admit that this year's campaign to inoculate millions of New Yorkers against poliomyelitis would never have been more than an idea, without the cooperation of scores of lay and allied medical organizations. Working with the doctors and nurses were industrial groups, labor unions, schools, public housing staffs, P.T.A.'s, and service clubs. Newspapers and broadcasting stations kept interest alive by repeatedly emphasizing the need for vaccinations, announcing sites for mass inoculations, and reporting progress of the county-wide program. Much of the

Salk serum was purchased by employers for their workers. Tens of thousands of hours were donated by lay volunteers as well as by medical personnel.

It was public service in action—but it also was top-notch medical public relations. The misconception that organized medicine is an ivory tower papered with greenbacks cannot survive in the shadowless light of a busy inoculation center—nor in the warm sunlight of a joint picnic of doctors, business executives, union stewards, ministers, and Kiwanis club boosters.

Just such an outing is routine in scattered parts of the nation—notably in Omaha, and Evansville, Ind., two cities where friendly intergroup dinner sessions are alternated with picnics. The Vandenburgh County Medical Society of Evansville goes one step farther in community identification. It pursues better interprofessional relations with dentists and druggists by joining them in annual session of baseball, skeet-shooting, poker-playing, or just plain shooting the breeze. The inevitable result is greater respect for each other's work. Dr. Louis H. Bauer, past-president of the A. M. A., sees an even broader benefit. He says: "The ready and constant willingness of the medical profession to take part in civic activities will be helpful to the community in solving health problems and will make the community ready to turn to the profession for advice rather than look to other, less qualified groups." This kind of willingness is rewarded in Columbus, Ohio (fig. 3).

Chambers of Commerce

No single lay organization has worked more closely with physicians in community affairs than the local chamber of commerce. Such liaison forms the backbone of community leadership for the Bronx County Medical Society. It is the basis for a recent decision of the Oakland (Calif.) Chamber of Commerce to create a permanent place on its board of directors for a medical representative (that "chamber" also helped finance the first diabetes fair ever held in the West). It is the reason that a chamber-encouraged "Business-Education Day" had physicians of the Parkersburg (W. Va.) Academy of Medicine taking over high school classes to inform youngsters what the profession was all about. And that sort of liaison is behind a Good Citizenship citation awarded to the Orleans Parish Medical Society by the New Orleans Chamber of Commerce for promoting a get-out-the-vote campaign.

Similar vote drives succeeded when the Michigan State Medical Society distributed 15,000 reminder leaflets to their patients and friends; when the South Dakota State Medical Association prepared "VOTE" napkins for restaurants in cooperation with a half dozen civic groups; and when the Medical Society of the State of New York sent its members this blunt note: "The doctor who doesn't vote . . . is not only letting down his profession, and all the men in public life who have championed medicine's cause; he is also letting down his country—and inviting destruction of the system he lives by."

Exception and Predominance

Certainly many an objective has been twisted out of kilter in the name of public service, and doctors are as keen as anyone else to recognize that even their profession is subject to "the exceptional case." Right now, for example, several of them are concerned with developments in a Western community where the leading doctor has a long record of active participation in local government. Not long ago a tradesman he had hired was injured in a fall down some stairs in the physician's home. Blaming his employer, the victim was taken to a local hospital, where he was treated by the same doctor—who later billed the tradesman for medical services. One sympathetic outsider suggested that the man take his troubles to the mayor. That doctor was also the mayor!

Public service to improve a community is a heroic task in itself, but when physicians team up with laymen to help bring about the very survival of their city—that is an epic accomplishment. It happened several years ago in Utica, N. Y. (population 101,500), where thousands of men were thrown out of work

Fig. 3.—Public service is recognized as the Metropolitan Health Council of Columbus and Franklin County presents certificates to five of its past presidents. The recipients, physicians of the Columbus Academy of Medicine, led programs for expansion of Ohio State University medical center, organization of a city hospital federation, setting up of a county-wide tuberculosis control program, creation of a city health department, and reorganization and planning of a child mental health clinic. Dr. Richard Meiling, president of the Ohio state medical association, presents certificates to Drs. Russel G. Means, James J. Hughes, John H. Mitchell, Robert Inglis, and Thomas Rardin.

in the mass shutdown of textile mills. Business leaders launched a bold plan to bring in electronics, toolmaking and metal-working industries and to train the unemployed in these new crafts. Every organization in town was asked to cooperate. Would the medical profession help encourage job applications by giving free physical examinations? The doctors would, and did.

Today, Utica is rescued from the doom of a ghost industrial city. Executive Secretary Harold N. Howell of the local Oneida County Medical Society offers this bit of understatement: "We were meeting our civic obligations as physicians."

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THE BIOLOGY OF AGING

GUEST EDITORIAL

George E. Wakerlin, M.D., Ph.D.

The concept that aging is an endogenous process inherent in all living things and not basically dependent on stress and disease is increasingly accepted, although we still do not have sufficient data to choose finally between these alternatives or to conclude that a cell, organ, or organism placed in an optimal environment may not live indefinitely. Gerontologists with a primary interest in pathology are perhaps more inclined to emphasize disease in relation to aging, but they may be biased, since they commonly see the end-result of illness requiring hospitalization. Certainly pathologists are unlikely to see the few persons who die essentially of uncomplicated old age. The fact that maintenance of various species of animals on a limited diet will prolong life through delaying sexual maturation and prolonging growth still constitutes the strongest support for the view that aging is an endogenous process—a product of reduced growth potential or insufficient rate of protoplasmic reduplication. On the basis of this interpretation, is there a possibility that the present tendency toward overnutrition of children in some parts of our Western world may lead to earlier maturity and a decreased life span? The accepted importance of internal and external stresses in accelerating the aging process is interestingly exemplified by the recent finding of more calcium and cholesterol in the arteries of the right side of the body of right-handed persons as compared with the left side.[1] Although stress and disease are probably not basic to aging, there is, of course, complete agreement that the minimizing or eradication of disease, particularly the degenerative diseases, will add many years to human life.

When we learn the basic mechanisms of aging, we may understand why various structures and functions of the human being reach their acme and begin to decline at different times in the life span. Thus aging begins with birth (or possibly conception) in terms of growth, with birth in relation to arterial elasticity, at 10 years of age in terms of acuity of hearing, at 15 years in relation to antibody production, and at 25 years in terms of neuromuscular function. Such data suggest that aging may be a multicentric phenomenon in man.

Life has been defined as an orderly functioning of enzymes, and ultimately aging will probably be explained in terms of intracellular enzyme changes that in turn produce tissue, organ, and body alterations in the direction of decreased reserve, adaptability, and homeostasis. Accordingly, a number of enzymes have been studied recently in relation to aging. With few exceptions the results have been disappointing, but certain leads have developed. Thus the fumarase content and phenolsulfatase activity of the human aorta have been shown to decrease with age.[2] Further studies of enzymes in relation to aging are urgently needed. This is also true for cell-membrane permeability.

It is highly important to distinguish between the appearance and results of aging and the fundamental processes of aging. Thus certain structural changes in cells that are known to occur with increasing age appear related primarily to cumulative stress. Other changes appear to be more definitely related to aging per se, such as the pigment of connective tissue and of nerve cells, particularly the large, ventral horn cells. However, complete separation of these factors is impossible, since the cells of the body must continually adjust themselves to alterations in their fluid environment. Neurones are well known as long-lived, nonreproducing cells that undergo histological changes with age and some of which die before the organism. Thus neurones show a gradual loss of Nissl substance from the cytoplasm, increasing basophilia of the nucleus, and loss of regularity of outline of nucleus and

From the University of Illinois College of Medicine, Chicago.

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cell body. Cardiac muscle shows a gradual decrease of nuclear mass and increasing pigment. The cellular and extracellular bases of aging in cartilage include asbestiform and albuminoid degeneration and, in bone, a predominance of resorptive over osteogenic processes. The glandular tissues vary considerably in the microscopic changes that they show with aging, and a better understanding of these differences may ultimately assist in solving the basic mechanism(s) of aging. Since there are definite decreases in the number of cells of various tissues with aging, the basic problem is one of determining the structural and functional differences between the cells that remain and those of younger individuals.

It is also important to determine whether the basic changes in aging are intracellular or extracellular, and to this end a study has been recently made of the chemical constitution of extracellular tissues.[3] The results show that, for the skin, lung, and femur of rats, fibrillar elements are deposited at a faster rate than the gel in which the fibrils lie. The relative increase in fibrils could impair the transfer of nutrients and metabolites to and from the cells of a given tissue. Work is presently under way to determine whether the gel-fibril ratio of a tissue may be used as a measure of age.

Study of so-called transient tissues should provide information of value to our understanding of aging.[4] The placenta is an example of a transient organ that has been extensively studied and is deserving of further investigation. Cytological and cytochemical changes involving nuclei and cytoplasm occur. Glycogen gradually disappears from the fetal placenta. The mitochondria of the yolk-sac epithelium become swollen and disorganized in the latter part of pregnancy. Cytoplasmic ribonucleoprotein decreases, whereas acid and alkaline phosphatases increase. As pregnancy advances, the mesenchyme of the villi becomes fibrotic. The endothelium of the spiral arteries of the endometrium becomes many-layered. Metabolically the placenta shows decreased activity as gestation proceeds, including consumption of oxygen, rate of utilization of glucose and pyruvate, and production of lactate. Red blood cells, the juxtamedullary zone of the adrenal cortex, ovarian tissues, and deer antlers have also been studied as examples of transient tissues. Leukocytes are deserving of continued attention in this connection. In relation to the ovary, recent work affirms the view that the ovary does not form new ova postnatally, and further work on the relation of the age of the ovum to longevity is desirable.

We must continue to study the changes of aging, tissue by tissue, organ by organ, and function by function, recognizing, however, that this method offers difficulties in experimental design and interpretation because of the many interrelations of function, particularly in higher organisms. Many such studies have been recorded, those listed below being relatively recent and in some cases refining and confirming older findings: 1. Studies of pulmonary function in man show decreased mobility of the chest wall and decreased elastic recoil of the lungs. Maximum voluntary ventilatory capacity, maximal inspiratory capacity, inspiratory reserve volume, expiratory reserve volume, and vital capacity are all decreased with increasing years. The capacity of the lung to ventilate the pulmonary blood is also slightly decreased. These changes, of course, are greatly exaggerated in pulmonary emphysema. 2. The excretion of 17-ketosteroids in the urine of the human being is significantly reduced with aging, particularly the non-11-oxygenated steroids. The radioactive iodine uptake and release from the thyroid are 20% less in old as compared with young rats. Presumably the reduction in thyroid secretion is a homeostatic adjustment to diminished target organ requirements and/or decreased inactivation of circulating hormone. The neurohypophysis of old rats, contrary to that of young animals, does not respond to a potent antidiuretic osmotic stimulus administered via the carotid artery.[5] 3. Reactions to stress are impaired in later years. Compensatory mechanisms minimize these physiological limitations, but more and more of these compensatory factors are called into play as age advances. In man, better preservation of function and more favorable reaction to stress are assisted by reasonable levels of mental and physical activity in later years. 4. There is a gradual decrease in the cardiac output of the human being with age. Young and old arterial elastins show a significant difference in amino acid composition, with a progressive increase in calcium

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content with age.[6] Preparations of intima and media of human thoracic aorta show increased diffusion of nitrogen, oxygen, carbon dioxide, lactate, iodide, and glucose with age.[7] Such vascular alterations as spider nevi, cherry angiomas, venous stars, and caviar-tongue lesions increase in frequency with age.[8] Further work may indicate whether they are the result of aging, of cumulative stresses, or of a combination. Careful consideration should be given to the probability that multiple pluggings of small blood vessels by agglutinated red blood cells that occur in disease and following injury may play an auxiliary role in aging, with successive destruction of histological units.[9] 5. The basal metabolic rate of the human being (measured by oxygen consumption) decreases with age in proportion to the decrease in amount of functioning protoplasm, measured by intracellular water. Total body water decreases with age due to decrease in intracellular water, without change in extracellular water. The amount of intracellular water is the same in old as in young cells.[10] Previously the view was widely held that the basal metabolic rate of the active tissues of the human shows a gradual decrease with age. 6. In the human being, there is a progressive decrease in renal blood flow, glomerular filtration rate, tubular excretory and resorptive capacities, and the ability of the renal tubule cells to perform osmotic work.[10] 7. There is a gradual but continuous decline in cerebral blood flow and oxygen consumption from the third decade through middle and old age. However, there appears to be no significant relationship between loss of mental acuity and decrease in these two factors.[11]

However, not all physiological processes go downhill with age. Thus, the bicarbonate content and the carbon dioxide tension of the plasma do not change significantly in man. This is also true for the arterial blood sugar level, blood volume, and the eosinophil response to corticotropin.[10]

New biological methods or older methods newly applied for studying the aging process may well supply important information. Thus the parabiotic union of old and young rats by combining the technique of retarded growth by limited diet and the production of successive litters from the same parents is under study. Homotransplantation of adrenal cortex from old rats into young rats for comparison with the effect of adrenal cortex from young rats enables study of aged adrenal cortical cells in a youthful environment. Tissues can be preserved by freezing and later thawing in vitro, so that cells and tissues from a young animal can be held for many months and then transplanted back into the aging donor. The rate of turnover of isotopes has already been referred to and should be increasingly used for gerontologic studies. Ionizing radiation accelerates the aging process in animals and may prove to be a valuable technique. A new suggestion, related to radiation, postulates that aging may be the result of deleterious effects of free radicals, such as OH and HO_2, on cell constituents and connective tissues.[12]

Biological research on aging is important not only for gerontology but for the geriatrics of tomorrow. Only through research can we achieve the prime goal of gerontology, which the Greeks indicated more than 2,000 years ago by pointing out that the art of living consists in dying young but as late as possible.

TO M.D. ADD P.S. (PUBLIC SERVANT)

How many hats do you wear in your town? Lots of physicians all over the country these days are wearing the extra hat of public service, and their impact on the community is tremendous, according to another Medicine at Work report on page 947. The article, "Double-Hatted Doctors Are Remaking Our Communities," points up the beneficial influence that physicians can exert when they join with other groups to get out the vote, campaign for greater safety, push for school improvments, or take part in other civic betterment programs.

All these "nonmedical" activities actually are linked to better health for the doctor's fellow citizens. But what is more, they are putting his practice into the proper perspective of many doing together what cannot be done alone or separately. In community activity, a physician finds his "whole" patient—individually and collectively—looking to him for leadership in an endeavor where service is a fruitful privilege, not a thankless task.

Thousands of doctors now are "finding the time" to serve on chambers of commerce, school boards, and better government committees. They are doing it in addition to more direct health service in care for the indigent and in volunteer disease control programs. By joining with businessmen, wage earners, and other laymen who also are donating their time and talents, these "good citizen doctors" are throwing the lie to the misconception that medicine is "an ivory tower papered with greenbacks."

THE DOCTOR IN RUSSIA

Elsewhere in this issue of THE JOURNAL (page 976) are excerpts from an article entitled "The Soviet Doctor's Dilemma," by Mark G. Field, which appeared in the January-February issue of the magazine *Problems of Communism*. Mr. Field is the author of several articles on the medical profession in the U. S. S. R. The article in question contains some interesting information on the status of the doctor in Russia, and it should provide considerable food for thought for those who believe that medical care in the United States should be taken out of the hands of physicians and their patients and placed under government control.

MEDICINE AND THE LAW

This is the sixth in a series of articles dealing with medical professional liability. An editorial (Page 360) and chronological résumé (Page 364) appeared in THE JOURNAL, *Feb. 2. One of the preceding articles in this series has been published each week in* THE JOURNAL, *beginning Feb. 9, 1957.*—ED.

HAZARDOUS FIELDS OF MEDICINE IN RELATION TO PROFESSIONAL LIABILITY

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Selection of hazardous fields in medicine is difficult since no aspects of the practice of medicine are free from hazard. The taking of an aspirin tablet may lead to death from hypersensitivity; the simple administration of a general anesthetic agent carries a mortality risk of one in 5,000; the setting of a fracture may lead to fatal fat embolism; penetration of the pleura in a simple therapeutic pneumothorax may produce circulatory collapse, at times fatal; and the administration of penicillin is producing fatal anaphylactic reactions in increasing frequency. Medicine is indeed a hazardous profession, and the yearly advances in the diagnosis and treatment of disease, despite the overall benefit to mankind, burden the physician with the danger of serious and irreparable damage to the patient in spite of the utmost care.

Two significant papers have appeared during the past year emphasizing the need of caution by the physician. In the Frank Billings Memorial Lecture of 1955 on the subject "Hazards of Modern Diagnosis and Therapy—the Price We Pay," Barr [1] presented a masterly dissertation on toxic reactions to drugs employed in both diagnostic and therapeutic medicine. In the medical progress section of the *New England Journal of Medicine*, Moser [2] recently discussed "Diseases of Medical Progress" and presented an extensive outline of reactions or complications, both medical and surgical, which produce new disease syndromes. It would be well for every physician to read these two papers with care and to reflect upon the dangers of new medications and surgical procedures.

Now, in a discussion of hazardous therapy, it is impossible to cover all hazards of modern medicine, surgery and drugs in detail. For such information the physician must refer to the textbooks, the medical literature, the instructions outlined in the manufacturers' brochures accompanying drugs or diagnostic agents, and information provided by evaluating bodies such as the A. M. A.'s Council on Drugs. He may also be guided by the experiences of other physicians and surgeons working in the field. Nevertheless, it is possible to review the subject in general fashion and to indicate to the physician those particularly hazardous fields in which he need observe special safeguards for the protection of the patient and for himself.

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The physician must first reemphasize his philosophy that no surgery should be performed nor should any medication be administered unless there is a clear-cut indication for the use of such procedure or medication. All efforts to establish a diagnosis must be exhausted before embarking upon medical or surgical treatment and conservative approaches in diagnosis and treatment should be utilized before radical and dangerous methods are employed.

Where are these particularly hazardous fields of medicine, especially those resulting in medical malpractice claims against the physician? A recent statistical review of such claims in California by me [3] indicates that they are mainly surgical in nature, accounting for 68% of all malpractice claims. The remaining cases are medical, and comprise toxic drug reactions, which are foremost, together with radiological equipment failures and accidental falls. Among the surgical cases, obstetrics and gynecology emerged in this study as the surgical branch leading in claims, with orthopedics next in line, and general surgery following. The surgeon must realize that he is particularly vulnerable. Likewise the physician must use medications with utmost caution to prevent toxic reactions. Both surgeon and physician must be alert to recognize as early as possible these complications and reactions and be cognizant of the proper steps to take in behalf of their patient.

While all medicine and surgery is necessarily hazardous, experience indicates that certain fields carry an unusually high degree of hazard. These may be considered as follows.

Hazards in Medical Field

The hazardous medical fields are both diagnostic and therapeutic in nature.

Diagnostic Injection Procedures.—Various diagnostic procedures, usually involving the instillation or injection of organic iodine compounds, are available for visualization [4] or functional testing of liver, gallbladder, urinary tract,[5] bronchi, lungs, heart,[6] blood vessels,[7] and spinal canal. In general, these organic agents may lead to anaphylactic reactions—sometimes fatal—despite the most careful pretesting for sensitivity, or may cause irritative phenomena leading to irreversible tissue damage. Of particular note is the problem set forth by the intravenous cholangiogram, intravenous pyelogram, angiogram, and the myelo-

gram. Even the intravenous injection of such an innocuous substance as dehydrocholic acid (Decholin) for circulation time may produce sudden death.

Acute Allergic Reactions.—The entire spectrum of allergic reactions from fever, rash, urticaria, lymphadenopathy, arthritis, and including the dreaded anaphylactic reaction may be seen with a wide variety of medications.[8] These medications may range from such seemingly nontoxic agents as aspirin and thiamine chloride to the antibiotics, notably penicillin. It is well established that these agents are more likely to cause serious and fatal reactions if given parenterally and less likely to do so if given by mouth. It is also well known that intravenous use is considerably more hazardous than intramuscular injection. Consequently, the physician should employ these agents by parenteral injection only when there is clear-cut evidence that use per os is not desirable or effective. The patient should be questioned as to prior use of the drug and as to evidence of previous allergic reaction to it. This is particularly true of penicillin since fatal anaphylaxis from this antibiotic seems to be increasing with alarming rapidity during the past several years. The dangers of tetanus antitoxin and other horse serum products are so well known that the point needs no further discussion.

Discussions of preliminary testing for sensitivity by conjunctival or intradermal methods [8] and the simultaneous injection of an antihistaminic agent [9] along with penicillin or other drugs are controversial. It does seem clear, however, that (1) such testing measures are not necessarily infallible and (2) the injection of an antihistaminic agent itself is not without danger. The physician must always be prepared to immediately treat anaphylactic shock should such appear in his office. While various agents such as parenteral hydrocortisone and antihistaminics and positive-pressure oxygen have been suggested, the immediate injection of a 1:1,000 aqueous epinephrine hydrochloride solution, in a dosage of 0.5 cc. intramuscularly or preferably 0.25 cc. intravenously, has stood the test of time. Until further clarification, the use of agents other than epinephrine probably should be considered as an ancillary procedure for the treatment of anaphylaxis.

Hemotoxic Drug Reactions.—A wide variety of drugs may cause serious reactions in the blood and blood-forming tissues with the production of pancytopenia, agranulocytosis, and hemolytic reactions.[10] Among this group of agents prominently mentioned should be the nitrogen mustards, sulfonamides, gold salts, antithyroid agents (thiouracil, propylthiouracil, and methimazole), certain antibiotics as chloramphenicol (Chloromycetin), phenylbutazone (Butazolidin), and various other drugs containing a benzene ring in combination with an amino or NH group. Even such commonly used and seemingly nontoxic agents as acetazolamide (Diamox),[11] chlorpromazine (Thorazine), and promazine (Sparine) [12] have recently been reported to lead to agranulocytosis.

Gastrointestinal Drug Reactions.—The effects of the broad-spectrum antibiotics upon the gastrointestinal system causing such severe reactions as pruritus ani and pruritus vulvae, liver damage, and pseudomembraneous enterocolitis are well known.[10] The use of antibiotic lozenges frequently produces a severe stomatitis. The use of chlorpromazine has led to the description of an infrequent jaundice characterized by intrahepatic cholestasis,[13] which in itself may not be dangerous or fatal but is differentiated with difficulty at times from carcinoma of the pancreas and consequently may lead to a needless exploratory laparotomy. Peptic ulcer, even with perforation, has not infrequently been described after the use of phenylbutazone.

Miscellaneous Drug Reactions.—Many other types of reactions to medications have been described but are too numerous to review in detail. The production of serious drug eruptions by gold salts, barbiturates, meprobamate (Equinil, Miltown),[14] acetazolamide,[15] and various types of ointments needs no elaboration. The reactions from the various adrenocorticosteroids with metabolic and electrolyte derangements, peptic ulcer, osteoporosis, hypertension, adrenal atrophy with adrenal exhaustion syndrome during stress such as operation, and indeed even anaphylactic shock with corticotropin (ACTH) [16] have been adequately described. The dangers of overmedication with antihistaminics are known. Very recently, the demonstration of an association between retrolental fibroplasia and high oxygen concentrations for premature infants [17] has led to a serious problem for the pediatrician and obstetrician.

Transfusions and Serum Hepatitis.—That serious reactions of all types may occur as a result of blood transfusions is well known, as is the transmission of serum hepatitis by means of blood transfusions, human plasma, or fibrinogen. It has been demonstrated that inadequately sterilized syringes or needles may transmit such hepatitis and experimental data now available indicate that routine autoclaving or boiling such equipment for periods up to 15 or 30 minutes must be employed to protect the patient.

Diathermy and Heat Lamps.—The relative frequency of claims against physicians for burns and injuries of this type makes it necessary for the physician to have qualified personnel in charge of such equipment and to have it in proper working order at all times.

Comment.—The physician must be reminded that the preceding discussion applies to a pitifully small group of potentially toxic drugs and procedures, and that the types of reactions described are indeed small in number. A description of all agents and all types of reactions is beyond the scope of this paper and the physician is again referred to other more detailed data,[8] the manufacturers' brochures, and publications such as New and Nonofficial Drugs and textbooks of pharmacology and therapeutics.

How Shall a Physician Protect His Patient and Himself Against These Reactions?—First, the indiscriminate overuse of medications must be avoided and there should be a demonstrable reason for the use of any drug. Second, there should be a concrete diagnosis, so the physician knows what he is actually treating. Third, the physician should utilize the less toxic agents before employing dangerous drugs if time and diagnosis permit. Fourth, the physician should adequately explain

these hazards to the patient before embarking on a therapeutic course since experience has demonstrated that the patient is less likely to criticize if he realized that there were hazards. Fifth, the physician should employ safeguards, both clinical and laboratory, to detect such toxic manifestations in their early stage before irreversible damage takes place.

Shock Therapy

The dangers of shock therapy,[18] electroshock or insulin shock, are principally those of induced fractures, cardiac arrhythmias, and myocardial infarction. These problems are well known to the expert in this field and need emphasis only from the standpoint of protection of the physician. First, there must be sufficient need demonstrated for such shock therapy. Second, it may be wise to routinely take x-rays before and after shock therapy of those parts of the skeletal system especially vulnerable to fractures such as the spine. Third, a careful cardiovascular survey including electrocardiogram is indicated in the case of the middle-aged patient. Fourth, the family should be warned of such possible complications of shock therapy if the patient is incompetent.

X-ray and Radium Therapy and Radioisotopes

X-ray and radium therapy is a traditionally hazardous type of medical practice, since tissue destruction and severe burns may necessarily result from treatment. It is basic that the physician doing such practice be well qualified in his subject, and that his apparatus and equipment be well metered and monitored. He must supervise his technicians carefully.

Patients should be bluntly acquainted with the possible dangers of irradiation before beginning such therapy, particularly when a heavy dosage is indicated. The signing of an acknowledgment of risk form or an exchange of letters may be desirable in certain instances. The following story is an example of how this may protect the radiologist. There was need for unusually heavy irradiation in a patient with pelvic carcinoma. The radiologist realized the possibility of a rather severe x-ray burn and so informed the patient. She agreed to accept this hazard but the radiologist elected to begin treatment a number of days later rather than immediately. On the same day of interview he dispatched a letter to the patient along the following lines, retaining a copy in his file. He had his secretary note in pen and ink the time of mailing and the post box in which the letter was deposited: "Dear Mrs.....: An appointment has been made to begin your x-ray treatments on next Tuesday, ... As I explained to you today in my office, the dosage of x-ray which will have to be employed in your case in an attempt to arrest the pelvic cancer will necessarily be so high it is probable that a serious x-ray burn will result. If you are willing to accept this hazard, please be present in my office on the appointed date so that we may begin your treatment."

The pelvic carcinoma was arrested, but a severe x-ray burn resulted, clearing after prolonged treatment. Nine months later, the radiologist received a letter from an attorney accusing him of negligence and improper care and demanding monetary remuneration for his client. When the radiologist's file, with the authenticated copy of the letter to the patient, was shown to the patient's attorney by the radiologist's attorney, the case was promptly dropped.

While the use of radioisotopes is potentially hazardous, practical experience up to the present does not indicate that this will become a serious problem,[19] possibly since the use of such materials is carefully supervised by the Atomic Energy Commission. Long-term professional liability problems, however, remain for the future to settle. Meticulous detail should be included in the medical records and they should be retained for the long-term future.

Surgical Procedures

All surgical procedures are hazardous but certain surgical procedures—particularly those in the diagnostic field—are more hazardous than usual reparative or curative surgery. These will be covered below.

A not infrequent question asked of the physician or surgeon by a patient is "Is this operation serious?" The time has long passed when the surgeon could pass off the dangers of an operation—whether tonsillectomy, appendectomy, cholecystectomy or other—by a favorable reply to put the patient at ease and free him of worry. Today, the physician or surgeon must honestly and bluntly inform the patient that all operations are serious and carry with them an irreducible number of complications regardless of the skill exercised by the surgeon. The surgeon must be prepared to elaborate on the complications if the patient so wishes. If a patient is not willing to accept such hazard, and has not been properly informed, the soil is nurtured for a malpractice suit when complications do occur, even if they are not the fault of the surgeon. Indeed, if the operation is a particularly hazardous one, the surgeon will do well to obtain an acknowledgment of risk statement from the patient or write a letter similar to the radiologist's letter. Sad but true, the time has come when we as physicians can no longer protect the complacency of the patient.

Aortograms and Angiography.—The performance of the aortogram and other types of angiography[20] is a hazardous diagnostic procedure even in the hands of the expert. Extravasation of dye, allergic reactions, tearing of the punctured vessel, thrombosis with causation of paralysis in the case of cerebral angiograms, and paraplegia with the aortogram, are well known and have been the subject of recent serious malpractice suits. Here again, the surgeon should make free disclosure preoperatively of the serious nature of these possibilities for his protection against blame for an uncontrollable result. Of course, the surgeon must be qualified in such procedures.

Myelograms.—Considerable controversy exists concerning the bona fide nature of complications following the myelogram. While certain irritative effects such as arachnoiditis have been described in the past with iodized oil (Lipiodol), universal agreement does not exist concerning such irritative changes. Until this point is settled by the use of the newer agents, the physician must be guided in the performance of the

myelogram by the basic need for the procedure and removal of the contrast medium as thoroughly as he can do it.

Lumbar and Cisternal Punctures.—The lumbar puncture is relatively free of hazard, although meningitis has been described from time to time. The cisternal puncture, on the other hand, is a dangerous procedure to be done only when necessary and when lumbar puncture cannot be used for one reason or another.

Anesthesiology.—The advances in the field of anesthesiology, while permitting the use of surgical procedures not feasible a decade or more ago, have created new hazards [21] with their new procedures and potentially toxic and dangerous agents. Insertion of the intratracheal tube may dislodge teeth and this frequently leads to claims.

Of additional interest and import is the use of caudal and spinal anesthesia, which, while doubtless the anesthesia of choice in certain operations and under certain conditions, carry with them dangers of reaction.[22] With caudal anesthesia, the inadvertent entrance into the spinal canal of a toxic dose of the anesthetic agent is known to cause sudden death, and hematomas may result from a tearing of certain blood vessels. With spinal anesthesia, the appearance of postoperative paresthesias and more important, the dreaded paraplegia from causes not yet entirely clear, has caused increasing anxiety in the anesthesiology field. A recent State Supreme Court ruling in California in the case of a cesarean section done under spinal anesthesia, which resulted in paraplegia, brought out two important points: 1. The obstetrician was released and the anesthesiologist and hospital were held. 2. The doctrine of *res ipsa loquitur* was applied, making such spinal anesthesia paraplegias well nigh indefensible in that state.

Defense of the physician-anesthesiologist in these spinal or caudal anesthesia complications rests upon the need for employing such methods of anesthesia in place of the more conservative inhalation methods.

The role of the anesthesiologist versus the surgeon in anesthesia accidents and complication is worthy of comment. There are three parties to be considered: the surgeon, the individual administering the anesthesia, and the hospital-employer. Where the anesthetist is a nurse (an employee of the hospital), it is clear that the hospital, the nurse-anesthetist, and the surgeon (as "captain of the ship") are jointly responsible. Where the anesthesia is administered by an anesthesiologist (physician-anesthetist) and further, where there is an employee or employee-like relationship between the anesthesiologist and hospital, then both anesthesiologist and hospital may be joined in an action. The place of the surgeon, where a physician-anesthesiologist gives the anesthesia, is not yet entirely clear but opinion seems to be swinging toward the view that the surgeon is free of responsibility. The California State Supreme Court ruling quoted above is indicative of this trend.

At any rate, the increasing number of physicians in anesthesiology over the past decade makes it clear that a new consultant—the anesthesiologist—has entered medicine. It is also apparent that the anesthesiologist deserves recognition as a consultant and is privileged to select the anesthetic agent of choice in consultation with the surgeon and in accordance with the medical status of the patient.

Cardiac Catheterization.—The new field of cardiac catheterization deserves mention. Such data as are available indicate that cardiac catheterization may produce serious disturbances in cardiac rhythm, even ventricular fibrillation sometimes leading to death.[23]

Needle Punch Biopsies.—Needle punch biopsies of the liver, spleen, other organs, and tumors carry a danger of tearing the organ and resulting in hemorrhage.[24] Such procedures should be done by qualified individuals utilizing conventional approaches and techniques to render the surgical diagnostic methods as free from hazard as is humanly possible.

Cosmetic Plastic Surgery and Scarring Dermatological Procedures.—Cosmetic plastic surgery and dermatological procedures that may lead to unsightly scars are hazardous not because they are a danger to life, but because the patient's appearance may be rendered unsightly and a sympathetic jury can see for themselves the untoward consequences. Such procedures on the face, neck, hands, or forearm, particularly in women, are especially litigation-prone. The dermatologist should undertake the removal of superficial skin growths only after notifying the patient of such possible scarring consequences. Both dermatologist and plastic surgeon should secure appropriate agreements in writing to this effect for their protection.

Orthopedics.—Every physician has been well indoctrinated as to the need for x-ray of the appropriate part of the skeletal system even in seemingly trivial injuries. The need for postreduction x-rays to show good alignment of fragments also should be emphasized. Failure to secure good results, functional or cosmetic, after setting of a fracture is important. When it is clear that good results either cannot be or are not being obtained, the early use of consultation is desirable for determination of the proper course to follow. Even the accomplished orthopedist should seek such consultation since the judgment of two physicians will survive under legal scrutiny better than one.

Obstetrics and Gynecology.—This seemingly nonhazardous field is emerging as a hazardous one from the standpoint of medical malpractice claims. The increased number of claims in this specialty chiefly concerns severed ureters and vesicovaginal fistulas following hysterectomy. While such complications are looked upon as necessary hazards to the operation, the malpractice charge may have merit if the reasons for the performance of the hysterectomy are inadequate since a complication would not have occurred if the operation had not been done. Obstetrics carries a dual hazard since the obstetrician has two potential claimants: mother and infant.

Experimental Medicine

The physician should keep abreast of progress in his field of medicine; he must utilize standard and recognized methods and medications in the treatment of his patients. In the treatment of a patient experimentation should be done only with the knowledge and consent of the patient or those responsible for him, and then only if the treatment does not vary too radically from the accepted method of practice.

The Federal Food, Drug, and Cosmetic Act prohibits the use of new drugs until there is evidence supporting the relative safety of the new agent. Not until then is the medication released for general use in the hospital or office, or by prescription or sale over the counter. Prior to this release, such drugs may be used only by experts qualified by scientific training and experience, and the law has established that such experimentation is done at the physician-investigator's peril.

The same principles apply to other types of experimentation, surgical as well as medical, and to conform to the ethics of the medical profession, ethical, legal and moral aspects must be observed as outlined by Regan.[25] The Judicial Council of the American Medical Association [26] has further stated three requirements: (1) the voluntary consent of the person on whom the experiment is to be performed; (2) the danger of each experiment must be previously investigated by animal experimentation; and (3) the experiment must be performed under proper medical protection and management.

Whether experimentation takes the form of investigation of new and unreleased drugs, transmission of disease entities, or experimental surgical procedures, a written and witnessed agreement between patient and physician is required. It should be understood by the physician that such a contract does not relieve him of the charge of negligence if reactions or complications occur, but does serve to indicate that such unconventional drugs or procedures were carried out with the knowledge and understanding of the patient.

Conclusions

Recitation of some of the daily hazards to which the physician is exposed may be frightening, but it serves to emphasize the fact that the physician of today is practicing a hazardous vocation. The problem of professional liability must be considered as an occupational hazard for every physician. Only by practicing with utmost diligence and care, observing conservative principles, and utilizing drugs and procedures that have stood the test of time, can the physician bring his untoward results and complications to their irreducible minimum. It is as important for the physician to know when not to treat as when to treat, and when not to employ the use of dangerous drugs and antibiotics as when to use these agents.

Some of the principles of prevention:

1. Exhaust all reasonable methods of study to secure a diagnosis before embarking on a therapeutic course.

2. Use the less dangerous methods of diagnosis before utilizing toxic agents or dangerous surgical procedures for diagnosis.

3. Use conservative and safe methods of medical treatment or surgical procedures before using highly toxic drugs or dangerous surgical procedures.

4. Use medical rather than surgical treatment wherever possible and use surgical procedures only when there is evidence that medical treatment is either undesirable, impossible, or ineffective.

5. Be sure of your qualifications before using hazardous medications or surgical procedures.

6. Read the manufacturer's circular or brochure accompanying an agent to be used for diagnostic or therapeutic uses, and, in addition, ascertain the customary dosage or usage in your area. If they vary, investigate further, and consult other authoritative sources of information in order to be sure of your ground.

7. When you are detailed on a new medication, ask for information on the known toxic manifestations and procedures to be employed to guard against such untoward reactions. If this seems deficient seek expert advice from other sources.

8. Know what the toxic manifestations may be of the drug you are using and what the proper methods of treatment are for such reactions.

9. Have your x-ray or other physical equipment properly metered and monitored.

10. Secure specific written consents and acknowledgments from the patient when using particularly hazardous drugs and diagnostic or surgical procedures.

11. Before you embark on experimental work, secure a witnessed written consent from the patient, be certain you are qualified to perform investigations in the field, and set up your experiment in true research style.

12. Do not use potent and toxic drugs and antibiotics for trivial complaints.

13. Use consultation freely before employing highly toxic drugs or exceedingly dangerous surgical procedures, particularly if the indications for these are not definite. Secure adequate consultations when reactions appear or complications occur.

14. Have sufficient and proper medical malpractice insurance coverage to prevent financial ruin if professional liability charges are brought against you.

459 30th St. (9).

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COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

INSTITUTIONS OFFERING SPECIAL TRAINING IN EXFOLIATIVE CYTOLOGY

The American Board of Pathology and the Council on Medical Education and Hospitals evaluate and recognize special training in exfoliative cytology as a part of programs in pathological anatomy.

The board has informed the Council that a trainee in pathology who receives special instruction in exfoliative cytology in such recognized programs may receive three-to-six-months' credit in pathological anatomy, depending on the nature of his other training in pathological anatomy. The board recognizes that approved programs in pathological anatomy offer training in exfoliative cytology concurrently with training in other phases of pathological anatomy. Therefore, special training in exfoliative cytology is not a requirement for eligibility for admission to the examination in pathological anatomy of the American Board of Pathology, even though exfoliative cytology has been and will continue to be a part of the examination in pathological anatomy.

The following institutions have been recognized by the American Board of Pathology as offering acceptable special training in exfoliative cytology. This list is published in order to make this information more generally available to those interested in training in this field.

1. University of California Hospital, San Francisco.
2. University of Colorado Medical Center, Denver.
3. Hartford Hospital, Hartford, Conn.
4. Yale University School of Medicine, New Haven, Conn.
5. Michael Reese Hospital, Chicago.
6. Vincent Memorial Laboratory, Massachusetts General Hospital, Boston.
7. New England Deaconess Hospital, Boston.
8. Free Hospital for Women, Brookline, Mass.
9. Mayo Clinic, Rochester, Minn.
10. The Jewish Hospital of St. Louis, St. Louis.
11. Washington University School of Medicine, St. Louis.
12. Cornell University Medical College, New York City.
13. Memorial Cancer Center, New York City.
14. The Roosevelt Hospital, New York City.
15. University Hospital of New York, University–Bellevue Medical Center, New York City.
16. St. Luke's Hospital, Cleveland.
17. Western Reserve University, Cleveland.
18. University of Oregon Medical School, Portland.
19. Jefferson Medical College, Philadelphia.

POSTGRADUATE COURSES

The following information regarding postgraduate courses for practicing physicians has been reported to the Council.

Ophthalmological Conferences

A seminar on aniseikonia and eikonometry will be held April 15-17 at the Bureau of Visual Science, American Optical Company, Southbridge, Mass. The 20-hour lecture, seminar, and open question-period course will have an enrollment limitation of 30 physicians specializing in ophthalmology, without tuition fee.

A similar conference, on the subjects of visual optics, refraction, indirect ophthalmoscopy, and subnormal vision, will be held at the Bureau of Visual Science, May 20-22. It is also limited in enrollment to 30 full-time specialists in ophthalmology.

Summer Clinics in Denver

The Ninth Annual Summer Clinics of the Children's Hospital, Denver, will be held June 24-26 for all physicians concerned with advances in medical knowledge regarding the care of children during the first few weeks of life. Educational methods include guest faculty with patient demonstration, live clinics, seminars, lectures, panel discussions, open question periods, and visual aids. There will be a total of 18 hours of instruction during the three days. Enrollment fee will be $25. For further information, contact the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18.

MEDICAL NEWS

CALIFORNIA

"The Most Happy Fella."—The setting for the Broadway musical hit, "The Most Happy Fella," now playing at the Imperial Theater in New York City, is in Napa, Calif., the hometown of A. M. A. President Dr. Dwight H. Murray. Keith Kaldenberg, the actor who plays the part of the general practitioner in the play recently met Dr. Murray backstage at the theater in New York before a performance. When the original play was made into the film, "They Knew What They Wanted," Dr. Murray was the doctor for the production crew when it was on location in Napa. The stars in the film were Clark Gable and Carol Lombard.

Backstage in the Imperial Theater, New York, Dr. Dwight Murray meets Keith Kaldenberg, actor in "The Most Happy Fella."

CONNECTICUT

Personal.—Dr. Lawrence S. Kubie, professor of psychiatry, Yale University School of Medicine, New Haven, recently delivered the Porter lectures at the University of Kansas School of Medicine, Lawrence–Kansas City. The lectures included "Neurotic and Creative Processes," "Scientific Creativity and the Learning Process," and "Art and Literature."

Appoint Surgeon-in-Chief.—Dr. Burr H. Curtis, Hartford, has been appointed surgeon-in-chief of the Home and Hospital for Crippled Children in Newington. He will continue a limited practice in Hartford in addition to his new position. Dr. Curtis has been a member of the Newington medical staff since 1941, and has been chairman of the staff for the past two years. In 1945 he was appointed assistant clinical professor of orthopedic surgery, Yale University School of Medicine.

GEORGIA

University News.—The Medical College of Georgia, Augusta, announces the appointment of Dr. Eldon L. Caffery, formerly lecturer at the University of Texas Postgraduate School of Medicine, Houston, as assistant professor of surgery (urology) and of Dr. John A. Owen Jr., as assistant professor of medicine.

Meeting on Ophthalmology and Otolaryngology.—The Georgia Society of Ophthalmology and Otolaryngology will hold its annual meeting at the General Oglethorpe Hotel in Savannah, March 21-23. The society's cruise, scheduled for May, has been canceled, as the cruise ship was sold to the Argentine government. The speakers originally scheduled for the program on the cruise have agreed to come for the meeting. Speakers will include Dr. Daniel C. Baker, New York City, Dr. G. Edward Maumenee, Baltimore, and others to be announced.

ILLINOIS

Anesthesiologists Meet in Chicago.—The Illinois Society of Anesthesiologists will meet at the Knickerbocker Hotel, Chicago, at 8 p. m., March 23. Dr. William O. McQuiston, Peoria, will serve as moderator for a symposium, "The Anesthesiology Resident Program." The panel members will be Dr. Ralph M. Tovell, chairman, department of anesthesiology, Hartford Hospital, Hartford, Conn.; Dr. Ivan B. Taylor, professor of clinical anesthesiology, Wayne State University College of Medicine, Detroit; Dr. Lawrence D. Ruttle, attending anesthesiologist, St. Joseph's Hospital and Silver Cross Hospital, Joliet; and Dr. Clifford A. Baldwin Jr., chairman, department of anesthesiology, Evanston Hospital, Evanston. Physicians are invited to attend.

Secretaries' Conference.—The Illinois State Medical Society will hold an all-day Secretaries' Conference at the Leland Hotel in Springfield, March 24. After the welcoming address by Lester Reavley, Sterling, president-elect, Illinois State Medical Society, Mr. Charles A. Carpentier, Secretary, State of Illinois, will speak on "Automobile Safety: A Problem." Edward Hamilton, Kankakee, a member of the Board of Trustees of the American Medical Association, will discuss "The Medicare Program and the Hospitalization of Non-Service Connected Veterans," and Frederick Slobe, Chicago, medical director, Blue Cross Plan, will discuss "Medicare" from the point of view of the fiscal administration. Charles L. Maxwell, Chicago, deputy director of health, Illinois Department of Civil Defense, will discuss "Civil Defense," and Earl H. Blair, chairman, Civil Defense Committee, Illinois State Medical Society, "What the Secretary Should Know About Civil Defense." Mr. Walter L. Oblinger, Springfield, associate counsel, Illinois State Medical Society, will speak on "Pending Legislation." The luncheon address will be presented by Austin Smith, Chicago, Editor of THE JOURNAL, who will speak on "Medicine! A Look at the Past and to the Future." In the afternoon, Harold Camp, secretary, Illinois State Medical Society, will moderate a panel discussion on the gen-

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

eral subject of the society's committee activities, with James Rutledge, Pittsfield; Fred A. Tworoger, Chicago; Hillard Shair, Quincy; Kenneth Scatliff, Chicago; and Jacob E. Reisch, Springfield, participating.

Chicago

Elliott Award to Dr. Allen.—Dr. J. Garrott Allen, professor of surgery, the University of Chicago School of Medicine, recently received the John Elliott award of the American Association of Blood Banks.

Meeting on Heart Disease.—The Chicago Heart Association and the Illinois Heart Association will offer the third annual scientific program on diseases of the heart, March 22, 2-9:30 p. m., at the Sheraton Hotel. The program will include discussion of pathogenesis and current trends in therapy for hypertension, rheumatic fever, coronary heart disease, congestive heart failure, and heart disease amenable to surgery. Dinner ($5.25 per plate including tax and gratuity) is scheduled for 6:30 p. m. For dinner reservations, call the Chicago Heart Association, 69 W. Washington St., FInancial 6-4675. The telephone for physicians' calls during the meeting is WHitehall 4-4100.

Summer Camp for Diabetic Children.—The Summer Camp for Diabetic Children will be opened for the eighth season under the auspices of the Chicago Diabetes Association from July 14 to Aug. 4 at Holiday Home, Lake Geneva, Wis. In addition to the camp personnel, the Chicago Diabetes Association furnishes resident physicians and dietitians, trained in the care of diabetic children. Boys and girls, ages 8 through 14 years, are eligible. Fees will be set on a sliding scale to meet individual circumstances. Physicians are urged to notify parents of diabetic children and to enter the names of children who would like to attend camp. Applications may be obtained from, and inquiries should be addressed to the Chicago Diabetes Association, 5 S. Wabash Ave., (ANdover 3-1861). Limited capacity makes prompt application advisable.

MARYLAND

Phi Delta Epsilon Lecture.—The annual lecture of the Phi Delta Epsilon fraternity of Baltimore will be given at 8:15 p. m., March 22, in Gordon Wilson Hall of the University Hospital, University of Maryland School of Medicine and College of Physicians and Surgeons. Dr. Paul H. Hoch, New York City, commissioner of mental hygiene of the state of New York, will have as his topic "The Use and Abuse of Tranquillizing Drugs." The paper will be discussed by Dr. Jerome D. Frank, professor of psychiatry, Johns Hopkins University School of Medicine, and John C. Krantz Jr., Ph.D., professor of pharmacology, University of Maryland School of Medicine and College of Physicians and Surgeons, both of Baltimore.

NEW YORK

New York City

Seventh Harvey Lecture.—"The Immunology of Transplantation," the seventh Harvey Lecture in the present series, will be delivered March 21, 8:30 p. m., at the New York Academy of Medicine, 103rd Street and Fifth Avenue, by P. B. Medawar, professor of zoology, University College, University of London.

Meeting on Oral Pathology.—The New York Institute of Clinical Oral Pathology invites members of the medical, dental, and allied professions to attend its monthly conference, March 25, 8:30 p. m. Brian E. D. Cooke, department of dental medicine, Guy's Hospital, London, will discuss "Fibro-Osseous Enlargements of the Jaws." The meeting will be in room 440 of the New York Academy of Medicine Building, 2 E. 103rd St.

OHIO

Medicolegal Institute on the Heart.—The Law-Medicine Center in Cleveland, a cooperative activity of Western Reserve University and the Cuyahoga County coroner's office, will present an institute on "The Heart: A Law-Medicine Problem," March 22-23. These sessions are designed to aid lawyers, doctors, claimsmen, personnel administrators, and labor union officials who handle personal injury litigation, workman's compensation, and rehabilitation matters involving injury and diseases of the heart and vascular system. Dr. Samuel R. Gerber, Cleveland, Cuyahoga County coroner, will serve as moderator. Registration (tuition $25) can be made through Prof. Oliver Schroeder Jr., director, The Law-Medicine Center, Western Reserve University, Cleveland 6.

SOUTH CAROLINA

Pressly Memorial Plaque.—The South Carolina Medical Association recently presented to the Medical College of the State of South Carolina, Charleston, a plaque honoring the memory of Dr. William L. Pressly, who served as president of the association in 1940 and who, in 1948, was designated "Family Doctor of the Year" by the American Medical Association.

Personal.—On the 50th anniversary of his graduation from the Citadel, Dr. William A. Smith, Charleston, was awarded an LL.D. degree by that institution. Dr. Smith has served as president of the South Carolina Medical Association, the Southern Sanatorium Association, Southern Tuberculosis Association, and the South Carolina Tuberculosis Association. He is clinical professor of medicine at the Medical College of South Carolina, Charleston, and chief consultant of Pinehaven Tuberculosis Hospital, where he was medical director for 30 years.

TENNESSEE

Oak Ridge Institute Given Deed to 38 Acres.—At the recent celebration of its 10th anniversary, the Oak Ridge Institute of Nuclear Studies, a nonprofit corporation of southern universities and colleges, operating under a contract with the U. S. Atomic Energy Commission, was presented with a deed for 38 acres of land. The plot is to be the site for permanent headquarters of the institute—a project still in the planning stage. Proposals for the contemplated development include an administration building, a technical library, dormitory and dining hall, quarters for the institute

medical division with a 34-bed hospital, a museum of atomic science, and technical shops. Construction is contingent on securing the necessary funds through grants from foundations and other nongovernment sources.

VIRGINIA

First Anderson Lecture at University.—The first John F. Anderson Memorial Lecture in Medicine was presented at the University of Virginia School of Medicine, Charlottesville, Dec. 17, 1956, by Dr. James A. Shannon, director, National Institutes of Health, U. S. Public Health Service, Bethesda, Md., on "Medical Research – 1956: Some Problems at Midcentury."

The Stoneburner Lectures at Richmond.—The 10th annual Stoneburner Lectures and Symposium on Therapy will be offered at the Baruch Auditorium, Medical College of Virginia, Richmond, March 20-22. The Stoneburner Lecturer, Selman A. Waksman, Ph.D professor of microbiology and director, Institute of Microbiology, Rutgers University, New Brunswick, N. J., will deliver the first lecture, "Antibiotics—Their Sociological and Economic Implications," at 8:30 p. m., Wednesday, and the second, "The Role of Antibiotics in Natural Processes," at the same time on Thursday. Out-of-state speakers for the symposium, which will be presented Thursday and Friday, will include Dr. Thomas B. Barnett, North Carolina School of Medicine, Chapel Hill; Dr. Harold E. Harrison, Johns Hopkins University School of Medicine, Baltimore; Dr. Frank L. Meleney, University of Miami, (Fla.) School of Medicine; Dr. Donald G. Johnson, Cornell University Medical College, New York City; and Dr. John P. Utz, National Institute of Allergy and Infectious Diseases, Bethesda, Md. There is no charge for the Stoneburner Lectures, but there will be a charge of $5 a day for the lectures given during the symposium, except to members of the faculty of the Medical College of Virginia, the medical department of the University of Virginia, the physicians of the McGuire Veterans Hospital, medical students, and members of the house staff of any hospital.

WEST VIRGINIA

Pediatric Meeting in Beckley.—The annual spring meeting of the West Virginia Pediatric Society will be held at the Beckley Hotel, in Beckley, March 23. A clinical case presentation at the Miner's Memorial Hospital in Beckley has been arranged for the morning of the meeting. Dr. John A. Kirkpatrick Jr., Temple University Hospital, Philadelphia, will show and discuss pediatric x-rays in the Beckley Hotel dining room beginning at 1:30 p. m. At 3:30 p. m., Dr. James B. Arey, St. Christopher's Hospital for Children, Philadelphia, will speak on "Pediatric and Pathological Misdiagnosis."

WISCONSIN

Create Chair of Medicine at Marquette.—The Francis D. Murphy Chair of Medicine has been created at Marquette University School of Medicine, Milwaukee. The endowment of $350,000, established anonymously by a Milwaukee donor, will honor Dr. Francis D. Murphy, present professor and director of the department of medicine, for 35 years of service devoted to the school. On Dr. Murphy's retirement, the full-time professor and director of the department of medicine will received his appointment through this endowment as the Francis D. Murphy Professor of Medicine.

CANADA

Surgeons Meet in Toronto.—The American College of Surgeons will hold a sectional meeting in Toronto, March 25-27, at the Royal York Hotel. The opening session will include a symposium on care of the patient with multiple injuries, which will be preceded by "Whiplash Injuries of the Neck" by Dr. Wallace P. Ritchie, St. Paul. The afternoon session will include "Primary Versus Secondary Repair of Tendons of the Hand" by Dr. Michael L. Mason, Chicago; "Nonmalignant Obstructions of the Common Bile Duct" by Dr. Stanley O. Hoerr, Cleveland; and "Urinary Complications of Rectal and Gynecological Surgery" by Dr. Reed M. Nesbit, Ann Arbor, Mich. A panel discussion, "Treatment of Peripheral Vascular Insufficiency," will have as moderator Dr. Wilfred G. Bigelow, Toronto, and as collaborators Drs. Fiorindo A. Simeone, Cleveland, and D. Emerick Szilagyi, Detroit. Panels have also been scheduled on bursitis and on amputations, and symposiums will be presented on treatment of the patient with advanced carcinoma; new developments in surgery; cataract surgery; and the role of radiology and radiotherapy in ophthalmology.

FOREIGN

Meeting on Allergology.—The Collegium Internationale Allergologicum will hold its third symposium March 25-29 at the Royal Society of Medicine in London. The main subjects are contact dermatitis versus atopic eczema and the gel-precipitation method and its applications in the field of allergy.

Message from Lady Whitby.—Lady Ethel Whitby, whose husband, Sir Lionel Whitby, died Nov. 24, 1956, has asked THE JOURNAL to express, on behalf of herself and her family, their warmest thanks to the many friends and colleagues of the late Sir Lionel who sent messages of sympathy and condolence.

CORRECTION

Book Review.—In the last book review on page 793 of THE JOURNAL, March 2, 1957, the third sentence of the second paragraph should have read: "Electrocardiography and radiography, while the latter is primarily considered physical diagnosis and not essentially a laboratory procedure, are included in the discussion. Laboratory procedures should not be expected to provide clinical diagnosis but to concur with clinical impressions derived from a carefully taken history and the physical examination where these two basic clinical techniques are not sufficient to prove beyond doubt the specific diagnosis entertained."

EXAMINATIONS AND LICENSURE

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 18-20. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery 4.

ARIZONA:* *Examination.* Phoenix, April 17-20. *Reciprocity.* Phoenix, April 20. Exec. Sec., Mr. Robert Carpenter, 826 Security Building, Phoenix.

ARKANSAS:* *Examination.* Little Rock, June 13-14. Sec., Dr. Joe Verser, Harrisburg.

CALIFORNIA: *Written Examination.* San Francisco, June 17-20; Los Angeles, Aug. 19-22; Sacramento, Oct. 21-24. *Oral Examination.* San Francisco, June 15; Los Angeles, August 17; San Francisco, Nov. 16. *Oral and Clinical for Foreign Graduates.* San Francisco, June 16; Los Angeles, Aug. 18; San Francisco, Nov. 17. Sec., Dr. Louis E. Jones, 1020 N St., Sacramento 14.

COLORADO:* *Reciprocity.* Denver, April 9. Final date for filing application was March 11. *Examination.* Denver, June 11-12. Final date for filing application is May 13. Exec. Sec., Miss Beulah H. Hudgens, 715 Republic Bldg., Denver 2.

DELAWARE: *Examination.* Dover, July 9-11. *Endorsement.* Dover, July 18. Sec., Dr. Joseph S. McDaniel, 225 S. State St., Dover.

DISTRICT OF COLUMBIA:* *Examination.* Washington, May 13-14. Deputy Director, Mr. Paul Foley, 1740 Massachusetts Ave., N. W., Washington.

FLORIDA:* *Examination.* Miami, June 23-25. Sec., Dr. Homer L. Pearson, 901 N. W. 17th St., Miami.

GEORGIA: *Examination and Reciprocity.* Augusta and Atlanta, June. Sec., Mr. Cecil L. Clifton, 111 State Capitol, Atlanta 3.

IDAHO: *Examination and Reciprocity.* Boise, July 8-10. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

ILLINOIS: *Examination and Reciprocity.* Chicago, Apr. 1-4. Supt. of Regis., Mr. Fredric B. Selcke, Capitol Bldg., Springfield.

INDIANA: *Examination.* Indianapolis, June 19-21. Exec. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

KANSAS: *Examination and Endorsement.* Kansas City, June 5-6. Sec., Dr. Lyle F. Schmaus, 864 New Brotherhood Bldg., Kansas City.

KENTUCKY: *Examination.* Louisville, June 10-12. Sec., Dr. Russell E. Teague, 620 S. 6th St., Louisville.

MARYLAND: *Examination.* Baltimore, June 18-21. Sec., Dr. Lewis P. Gundry, 1215 Cathedral St., Baltimore 1.

MASSACHUSETTS: *Examination and Endorsement.* Boston, July 9-12. Sec., Dr. Robert C. Cochrane, 37 State House, Boston 33.

MICHIGAN:* *Examination.* Ann Arbor and Detroit, June. Sec., Dr. E. C. Swanson, 118 Stevens T. Mason Bldg., West Michigan Ave., Lansing 8.

MINNESOTA:* *Examination.* St. Paul, April 16-18. Sec., Dr. F. H. Magney, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: *Examination.* Jackson, June 24-25. *Reciprocity.* Jackson, June 26. Asst. Sec., Dr. R. N. Whitfield, Old Capitol, Jackson.

MONTANA: *Examination and Reciprocity.* Helena, Apr. 2-3. Sec., Dr. S. A. Cooney, 214 Power Block, Helena.

NEBRASKA:* *Examination.* Omaha, June 17-19. Director, Mr. Husted K. Watson, Room 1009, State Capitol Bldg., Lincoln 9.

NEVADA:* *Examination and Reciprocity.* Reno, April 2. Sec., Dr. G. H. Ross, 112 North Curry St., Carson City.

NEW JERSEY: *Examination.* Trenton, June 18-21. Sec., Dr. Patrick H. Corrigan, 28 West State St., Trenton.

NEW MEXICO:* *Examination and Reciprocity.* Santa Fe, May 20-21. Sec., Dr. R. C. Derbyshire, 227 E. Palace Ave., Santa Fe.

NEW YORK: *Examination.* Albany, Buffalo, New York and Syracuse, Feb. 5-8. Sec., Dr. Stiles D. Ezell, 23 S. Pearl St., Albany.

NORTH CAROLINA: *Endorsement.* Asheville, May 5, and Raleigh, June 18. *Written Examination.* Raleigh, June 17-20. Sec., Dr. Joseph J. Combs, Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, July 10-13. *Reciprocity.* Grand Forks, July 13. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Endorsement.* Columbus, April 1. *Examination.* Columbus, June 13-15. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus.

OKLAHOMA:* *Examination.* Oklahoma City, June 11-12. Sec., Dr. E. F. Lester, 813 Braniff Building, Oklahoma City.

OREGON:* *Examination.* Portland, April 19-20. Office of the Board, 609 Failing Bldg., Portland.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July 10-12. Acting Sec., Mrs. Marguerite G. Steiner, Box 911, Harrisburg.

RHODE ISLAND:* *Endorsement.* Providence, March 28. *Examination.* Providence, April 4-5. Administrator, Mr. Thomas B. Casey, 306 State Office Bldg., Providence.

SOUTH CAROLINA: *Endorsement.* Myrtle Beach, April 30. *Examination.* Columbia, June 25-26. Sec., Mr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination and Reciprocity.* Place not yet determined, July 16-17. Sec., Dr. C. B. McVay, Yankton Clinic, Yankton.

TENNESSEE:* *Examination.* Memphis, March 27-28. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis 3.

TEXAS:* *Examination and Reciprocity.* Fort Worth, June 24-26. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 11-13. Director, Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

VIRGINIA: *Reciprocity.* Richmond, June 12. *Examination.* Richmond, June 13-15. Office of the Board, 631 First St., S. W., Roanoke.

WEST VIRGINIA: *Examination.* Charleston, April 22. Sec., Dr. Newman H. Dyer, State Office Bldg. No. 3, Charleston 5.

WISCONSIN:* *Reciprocity.* Madison, April 26. *Examination.* Milwaukee, July 9-11. Sec., Dr. Thomas W. Tormay, Jr., 1140 State Office Bldg., Madison 2.

WYOMING: *Examination and Reciprocity.* Cheyenne, June 3. Sec., Dr. F. D. Yoder, State Office Bldg., Cheyenne.

ALASKA:* On application in Anchorage and Juneau. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

GUAM: *Subject to Call.* Act. Sec., Dr. S. F. Provencher, Agana.

PUERTO RICO: *Examination.* San Juan, March 5-9. Sec., Mr. Joseph Mercado Cruz, Box 9156, Santurce.

VIRGIN ISLANDS: *Endorsement.* St. Thomas, June 12. Sec., Dr. Earle M. Rice, St. Thomas.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: *Examination and Reciprocity.* Tucson, March 19, Sec., Mr. Herbert D. Rhodes, University of Arizona, Tucson.

ARKANSAS: *Examination.* Little Rock, May 6-7. Sec., Mrs. S. C. Dellinger, Zoology Department, University of Arkansas, Little Rock.

DISTRICT OF COLUMBIA: *Examination.* Washington, April 22-23. Deputy Director, Mr. Paul Foley, 1740 Massachusetts Ave. N. W., Washington 6.

FLORIDA: *Examination.* Miami, June 8. Sec., Mr. M. W. Emmel, Box 340, University of Florida, Gainesville.

IOWA: *Examination.* Des Moines, April 9. Sec., Dr. Ben H. Peterson, Coe College, Cedar Rapids.

MICHIGAN: *Examination.* Detroit and Ann Arbor, May 10-11. Sec., Mrs. Anne Baker, 116 Stevens T. Mason Bldg., W. Michigan Ave., Lansing 15.

NEBRASKA: *Examination.* Omaha, May 7-8. Director, Mr. Husted K. Watson, Room 1009, State Capitol Bldg., Lincoln 9.

NEVADA: *Examination.* Reno, April 2. Sec., Dr. Donald G. Cooney, Box 9005, University Station, Reno.

NEW MEXICO: *Reciprocity.* Santa Fe, April 7. *Examination,* Santa Fe, April 14. Sec., Miss M. Cantrell, Box 1522, Santa Fe.

OKLAHOMA: *Examination.* Oklahoma City, April 19-20. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

SOUTH DAKOTA: *Examination.* Vermillion, June 7-8. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

TENNESSEE: *Examination.* Memphis and Nashville, March 20-21. Sec., Dr. O. W. Hyman, 62 S. Dunlap Ave., Memphis 3.

TEXAS: *Examination.* Austin, April 12-13. Sec., Bro. Raphael Wilson, 407 Perry-Brooks Bldg., Austin.

WISCONSIN: *Examination.* Madison, April 6, and Milwaukee, June 1. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

ALASKA: *Examination and Reciprocity.* Anchorage and Juneau, first week of February, April, June, August and November. Sec., Dr. C. Earl Albrecht, Box 1931, Juneau.

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*Basic Science Certificate required.

DEATHS

Martin, James Reid ✱ Philadelphia; born in 1886; Jefferson Medical College of Philadelphia, 1910; in 1913 joined the department of orthopedic surgery at his alma mater, where he was assistant professor of orthopedic surgery from 1930 to 1938 and James Edwards professor and head of the department of orthopedic surgery from 1939 to 1950, when he became professor of orthopedic surgery emeritus and associate dean; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons; served overseas during World War I; consultant in orthopedic surgery at the Pottsville Hospital in Pottsville, the Chambersburg Hospital in Chambersburg, and the Memorial Hospital; at one time chief surgeon at the State Hospital for Crippled Children in Elizabethtown; died in the Jefferson Medical College Hospital Dec. 26, aged 70.

Beardsley, Edward John Gillespie, Philadelphia; Jefferson Medical College of Philadelphia, 1902; specialist certified by the American Board of Internal Medicine; an associate member of the American Medical Association; member of the American Clinical and Climatological Association; fellow and at one time governor of the American College of Physicians; served as secretary of the American Association of the History of Medicine and as vice-president of the American Congress on Internal Medicine; formerly clinical professor of medicine at the Jefferson Medical College and professor and head of the department of medicine at Woman's Medical College of Pennsylvania; veteran of World War I; for many years medical director of the municipal court; killed when he, aged 77, was struck by an automobile, Dec. 27.

Brook, Jacob Daniel ✱ Grandville, Mich.; born in Cleveland in 1876; Detroit College of Medicine, 1902; member of the House of Delegates of the American Medical Association from 1917 to 1938; past-president and vice-president of the Michigan State Board of Registration in Medicine; past-president of the Michigan State Medical Society, Michigan Public Health Association, Kent County Medical Society, and the Grand Rapids Academy of Medicine; served as county health officer; member and past-president of the board of education; an honorary member of the Grandville Rotary Club; member of the staffs of the Blodgett Memorial and Butterworth hospitals, Grand Rapids, and of St. Mary's Hospital, Grand Rapids, where he died Dec. 13, aged 80, of coronary occlusion.

Mood, George McFarlane ✱ Charleston, S. C.; born in Charleston March 18, 1880; Medical College of the State of South Carolina, Charleston, 1901; professor emeritus of bacteriology and preventive medicine at his alma mater, where in 1909 he became assistant professor of pathology and bacteriology, serving until 1911, when he became professor of pathology and bacteriology, and in 1912 became professor of bacteriology and preventive medicine; formerly bacteriologist for the city and county departments of health; past-president of the Charleston County Tuberculosis Association; for many years associated with the Roper Hospital, where he died Jan. 10, aged 76, of an acute infection of undetermined origin with pneumonitis and empyema.

Knowles, Frank Crozer, Wynnewood, Pa.; born in Philadelphia Jan. 26, 1881; University of Pennsylvania Department of Medicine, Philadelphia, 1902; professor of dermatology emeritus at Jefferson Medical College, Philadelphia, where he was professor of dermatology since 1919 and where on April 28, 1939, the senior class presented his portrait; past-president of the American Dermatological Association; an associate member of the American Medical Association; specialist certified by the American Board of Dermatology and Syphilology; veteran of World War I; died in the Jefferson Medical College Hospital, Philadelphia, Jan. 9, aged 75, of multiple myeloma.

Royal, Paul Ambrose ✱ Lincoln, Neb.; born in Des Moines, Iowa, Jan. 17, 1891; State University of Iowa College of Homeopathic Medicine, Iowa City, 1915; specialist certified by the American Board of Psychiatry and Neurology; fellow of the American Psychiatric Association; veteran of World Wars I and II; past-president of the Lancaster County Medical Society; president of the Nebraska Psychiatric Society; on the staff of the Dr. Benjamin F. Bailey Sanatorium; consultant in psychiatry and neurology at the Veterans Administration Hospital; died in the Bryan Memorial Hospital Dec. 26, aged 65, of rupture of the myocardium and coronary thrombosis with infarction.

Stoops, Robert Earl ✱ Captain, U. S. Navy, retired; Conneaut, Ohio; born in Lebanon, Ind., Dec. 11, 1878; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1902; entered the regular U. S. Navy Jan. 27, 1904 and retired Jan. 1, 1943; awarded the Mexican Service medal and the World War I Victory medal; member of the Association of Military Surgeons of the United States; in 1937 member of the House of Delegates of the American Medical Association; fellow of the American College of Surgeons; died in the U. S. Naval Hospital, Bethesda, Md., Dec. 27, aged 78, of arteriosclerotic heart disease.

Farnsworth, Earle Edwin, Grand Island, Neb.; born in Middlebury, Vt., in 1881; Harvard Medical School, Boston, 1912; also a graduate in pharmacy; an associate member of the American Medical Association; at one time vice-president of the Nebraska State Medical Association; past-president of the Hall County Medical Society; fellow of the American College of Physicians; past-president of the Hall County Medical Society; on the honorary staff of St. Francis Hospital; a charter member and past-president of the Grand Island Rotary Club; died Dec. 31, aged 75, of spindle cell sarcoma of the vertebra.

✱ Indicates Member of the American Medical Association.

Johnson, Edward Sooy ✠ Baltimore; born Jan. 8, 1886; University of Maryland School of Medicine, Baltimore, 1912; associate professor of surgery at the University of Maryland School of Medicine and College of Physicians and Surgeons; member of the founders' group of the American Board of Surgery; fellow of the American College of Surgeons; consultant, St. Joseph's Hospital; on the staffs of the West Baltimore General, University, Franklin Square, South Baltimore General, and Mercy hospitals and the Church Home and Hospital; veteran of World War I; died Dec. 24, aged 70, of coronary thrombosis.

Langdon, Roy Luther ✠ Philadelphia; born in Lebanon, Pa., in 1892; University of Pennsylvania School of Medicine, Philadelphia, 1917; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; formerly associate professor of medicine at the Temple University School of Medicine; veteran of World War I; served as director of medical service and administrator, medical department, Germantown Dispensary and Hospital and chief of medical service at the Chestnut Hill Hospital; died Dec. 21, aged 64.

Samples, John Tilden ✠ Boonville, Ind.; born May 9, 1877; Kentucky School of Medicine, Louisville, 1907; veteran of World War I; served as president and secretary of the Warrick County Medical Society; for many years county health officer and medical examiner of the Veterans Administration of Warrick County; examiner for Warrick County Draft Board prior to and during World War II; almost 50 years on the staff of the Protestant Deaconess Hospital in Evansville, where he died Nov. 1, aged 79, of arteriosclerotic heart disease and cerebral thrombosis.

Bachmann, Robert Alexander, New York City; Rush Medical College, Chicago, 1900; served as a medical officer in the U. S. Coast Guard; later transferred to the U. S. Navy Medical Corps, from which he retired with the rank of commander in 1919; while on leave of absence from the Navy in 1910, was temporarily associated with the American Hospital in Paris; on his return to duty in the United States was attached to the Naval Torpedo Station, Newport, R. I.; fellow of the American College of Surgeons; died Jan. 5, aged 77.

Aiken, Thomas Gerald ✠ Berwyn, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1907; specialist certified by the American Board of Otolaryngology; member of the board of directors of the Chester County Hospital, West Chester, where he died Dec. 22, aged 72, of adenocarcinoma of the rectum.

Anders, Andrew, Lansdale, Pa.; Medico-Chirurgical College of Philadelphia, 1909; at one time on the faculty of the University of Pennsylvania Graduate School of Medicine in Philadelphia; veteran of World War I; died Jan. 9, aged 79, of cerebral vascular accident and arteriosclerosis.

Ashton, Frederick B. ✠ Highland Park, Mich.; Detroit College of Medicine, 1907; on the emeritus staff of the Highland Park General Hospital; died in Royal Oak Nov. 28, aged 79, of myocardial failure and cerebral hemorrhage.

Atkins, James Albert ✠ Columbia, Mo.; Harvard Medical School, Boston, 1932; instructor in pathology at the University of Missouri School of Medicine; veteran of World War II; at one time on the staff of the Veterans Administration Hospital in Muskogee, Okla.; on the staff of the Boone County General Hospital; died in the University Hospitals Dec. 19, aged 49, of cerebral hemorrhage.

Austin, Gerald John ✠ Bell Gardens, Calif.; University of Southern California School of Medicine, Los Angeles, 1949; for a short time served in the Medical Corps of the U. S. Naval Reserve; died Dec. 30, aged 32.

Baker, Lyle Lee ✠ Wood River, Ill.; University of Tennessee College of Medicine, Memphis, 1927; served on the staffs of the Wood River Township Hospital and the Alton Memorial Hospital in Alton; died Dec. 25, aged 60.

Ballard, Cora Marie, Hancock, N. Y.; Eclectic Medical College of the City of New York, 1898; an associate member of the American Medical Association; died in Binghamton Jan. 12, aged 91.

Bane, Clinton Eugene ✠ Mather, Pa.; University of Pittsburgh School of Medicine, 1918; on the courtesy staff of the Greene County Memorial Hospital in Waynesburg; died Dec. 31, aged 62, of uremia and chronic nephritis.

Bauer, Louis ✠ St. Louis; Washington University School of Medicine, St. Louis, 1930; died Dec. 29, aged 54, of a heart attack.

Berauer, Joseph Martin, Encino, Calif.; Medical College of Ohio, Cincinnati, 1893; an associate member of the American Medical Association; honorary member of the staff of the Queen of Angels Hospital, Los Angeles, where he was active on the staff for many years; died Dec. 22, aged 89.

Bing, Roland Eward ✠ Oakwood, Texas; University of Tennessee Medical Department, Nashville, 1909; died Dec. 22, aged 70.

Blum, Leo Jacob, Jr. ✠ Warner Robins, Ga.; Washington University School of Medicine, St. Louis, 1939; member of the American Academy of General Practice; veteran of World War II; died in the Middle Georgia Hospital, Macon, Dec. 8, aged 43, of coronary thrombosis.

Bollinger, Isaac Wesley ✠ Henryetta, Okla.; University of Arkansas School of Medicine, Little Rock, 1912; member of the Industrial Medical Association; veteran of World War I; medical director of the Henryetta Hospital; died Nov. 28, aged 67.

Boone, Malcome Alvah ✠ Dallas, Texas; Memphis (Tenn.) Hospital Medical College, 1898; University of the South Medical Department, Sewanee, Tenn., 1899; died in St. Paul's Hospital Nov. 23, aged 81.

Breed, Nathaniel Pope ✠ Lynn, Mass.; Harvard Medical School, Boston, 1901; fellow of the American College of Surgeons; served as chairman of the school committee; veteran of World War I; at one time medical examiner for the Ninth Essex District; formerly chief surgeon of Lynn Hospital; died Dec. 20, aged 82.

Britt, James Norment ✱ Lumberton, N. C.; Atlanta (Ga.) Medical College, 1914; past-president of the Robeson County Medical Society; on the staff of the Robeson County Memorial Hospital; died Dec. 24, aged 68, of carcinoma of the soft palate.

Brown, Clarence Emanuel, Faith, N. C.; North Carolina Medical College, Charlotte, 1918; member of the American Academy of General Practice; past-president of the Rowan County Medical Society; formerly county coroner; served on the staff of the Rowan Memorial Hospital in Salisbury; vice-president and director of Farmers and Merchant Bank of Granite Quarry; died Dec. 23, aged 64, of carcinoma of the cecum.

Brown, Elvin Otis ✱ Sacramento, Calif.; Chicago College of Medicine and Surgery, 1909; veteran of World War I; senior staff member of the Sutter General Hospital, where he died Dec. 30, aged 73.

Brown, Phyllis White, Fullerton, Calif.; University of Minnesota Medical School, Minneapolis, 1953; certified by the National Board of Medical Examiners; an associate member of the American Medical Association; died Dec. 6, aged 28.

Burth, Henry Herman, Jamaica, N. Y.; University of Buffalo School of Medicine, 1929; died in the Queens General Hospital Nov. 26, aged 57, of arteriosclerotic heart disease.

Ciemins, Janis ✱ Cleveland; Latvijas Universitāte Medicinas Fakultate, Riga, Latvia, 1930; died in St. Luke's Hospital Dec. 22, aged 50, of cerebral hemorrhage.

Coutu, George Octave, Burlington, Vt.; School of Medicine and Surgery of Montreal, Canada, 1901; died in the Bishop DeGoesbriand Hospital Dec. 23, aged 81, of arteriosclerosis.

Dahleen, Henry Ephraim ✱ San Jose, Calif.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1908; member of the staff of Mayo Foundation in Rochester, Minn., from Nov. 1, 1917 to July 1, 1920; for many years superintendent of the Santa Clara County Hospital; served on the staffs of the O'Connor Hospital and the San Jose Hospital, where he died Dec. 17, aged 74, of coronary occlusion.

Decker, Walter Joseph, Westfield, Pa.; Washington University School of Medicine, St. Louis, 1923; specialist certified by the American Board of Otolaryngology; an associate member of the American Medical Association; member of the Medical Society of the State of New York; formerly on the staff of the Mayo Foundation in Rochester, Minn.; served on the staff of St. Joseph's Hospital in Elmira, N. Y.; died in Wilkes-Barre Dec. 5, aged 62.

de Mailly, Robert Gilles ✱ San Francisco; Stanford University School of Medicine, San Francisco, 1944; clinical instructor in obstetrics and gynecology at his alma mater; interned at the Stanford University Hospitals, where he served a residency; specialist certified by the American Board of Obstetrics and Gynecology; served in the U. S. Naval Reserve; shot and killed Jan. 16, aged 39.

Doray, Frank Leslie ✱ Northboro, Mass.; Harvard Medical School, Boston, 1902; for many years practiced in Worcester; died in the Marlborough Hospital, Marlboro, Dec. 22, aged 86.

Dove, William B. ✱ Macon, Ga.; Fort Wayne College of Medicine, Fort Wayne, Ind., 1892; died in the Middle Georgia Hospital Dec. 12, aged 86, of cerebral hemorrhage.

Downing, James Arthur ✱ Des Moines, Iowa; Drake University College of Medicine, Des Moines, 1909; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Broncho-Esophagological Association, and the American College of Chest Physicians; on the staff of the Iowa Methodist Hospital, where he died Dec. 14, aged 69, of arteriosclerotic heart disease.

Easton, James William ✱ Superior, Wis.; Northwestern University Medical School, Chicago, 1939; served overseas during World War II; colonel, Illinois National Guard; physician for the Wisconsin State College; on the staffs of St. Mary's and St. Joseph's hospitals; died Dec. 16, aged 45, of coronary sclerosis.

Erickson, Oscar Leonard ✱ Topeka, Kan.; Kansas Medical College, Medical Department of Washburn College, Topeka, 1912; died Jan. 4, aged 68.

Feilchenfeld, Harry ✱ Blackwood, N. J.; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, 1923; on the staff of the Camden County General Hospital; died Jan. 8, aged 58.

Flehinger, Benno, New York City; Ludwig-Maximilians-Universität Medizinische Fakultät, München, Germany, 1923; member of the Medical Society of the State of New York; associated with the Beth David Hospital; died in the Presbyterian Hospital Dec. 6, aged 60, of cancer.

Flynn, Helen B., Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1906; died Sept. 15, aged 74.

Follis, James Robert, Memphis, Tenn.; University of Tennessee College of Medicine, Memphis, 1947; served during World War II; resident in radiology at the Veterans Administration Hospital (Kennedy), where he died Dec. 20, aged 40, of carcinoma of the rectum with metastasis.

Fowler, David D. ✱ Paint Rock, Texas; Metropolitan Medical College, Chicago, 1898; veteran of World War I; died in the Big Spring State Hospital in Big Spring Nov. 21, aged 85.

Franken, Carl C., New York City; University College of Medicine, Richmond, Va., 1910; an associate member of the American Medical Association; died Jan. 8, aged 82.

Frayser, William Nule ✱ Macon, Ga.; Meharry Medical College, Nashville, Tenn., 1916; veteran of World War I; on the staff of St. Luke Hospital, where he died Dec. 17, aged 65, of acute myocarditis and acute nephritis.

Freedman, Abraham Albert ✦ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1912; died in the Belmont Community Hospital Oct. 30, aged 66.

Garcia, Louis Joseph ✦ Tampa, Fla.; Georgetown University School of Medicine, Washington, D. C., 1931; member of the American Trudeau Society; veteran of World War II; formerly associated with the tuberculosis clinic of the city health department; on the staff of St. Joseph's Hospital; died Dec. 23, aged 52, of a heart attack.

Gentry, Charles Wofford, Greenville, S. C.; University of Maryland School of Medicine, Baltimore, 1903; veteran of the Spanish-American War and World War I; died Dec. 30, aged 79.

Gilliam, James C. ✦ Des Arc, Ark. (licensed in Arkansas in 1903); died in the Hawkins Clinic Hospital, Searcy, Dec. 11, aged 91, of pneumonia and congestive heart disease.

Goss, Forest Zeno, Picayune, Miss.; Medical Department of Tulane University of Louisiana, New Orleans, 1905; veteran of World War I; died Oct. 16, aged 76, of hypostatic pneumonia and carcinoma of the stomach.

Greenfield, Nathaniel Louis ✦ Cranbury, N. J.; Medizinische Fakultät der Universität, Vienna, Austria, 1938; veteran of World War II; on the staffs of the Roosevelt Hospital in New York City and the Princeton Hospital in Princeton; died Jan. 11, aged 50, of coronary arteriosclerosis.

Grigg, John Richard ✦ Lake Charles, La.; University of Louisville (Ky.) School of Medicine, 1927; on the staffs of the St. Charles Memorial and St. Patrick's hospitals; died Dec. 16, aged 58, of acute myocardial infarction.

Hall, Henry Martyn, Jr., Pittsburgh; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1897; an associate member of the American Medical Association; one of the founders of the National Tuberculosis Association; died Jan. 9, aged 84.

Hamilton, Luke Munro ✦ Oakland, Calif.; Stanford University School of Medicine, San Francisco, 1930; died Dec. 13, aged 53.

Hammer, A. Wiese, Philadelphia; Medico-Chirurgical College of Philadelphia, 1901; an associate member of the American Medical Association; fellow of the American College of Surgeons; on the staff of St. Luke's and Children's Medical Center; died in the Graduate Hospital of the University of Pennsylvania Dec. 27, aged 79, of cardiovascular disease.

Harris, Downey Lamar ✦ St. Louis; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1899; city bacteriologist from 1903 to 1907; formerly on the faculty of St. Louis University School of Medicine; veteran of World War I; served on the staffs of the St. Louis City, St. Anthony's, and Jewish hospitals; at one time associated with the U. S. Public Health Service; died in Clayton Dec. 23, aged 81, of coronary occlusion.

Hogan, Garrett Lansing, Beverly Hills, Calif.; Albany (N. Y.) Medical College, 1887; died Dec. 31, aged 93.

Hooe, Robert Arthur ✦ Washington, D. C.; George Washington University School of Medicine, Washington, D. C., 1906; member of the American Urological Association; on the staffs of the District of Columbia General and Freedmen's hospitals, and the Central Dispensary and Emergency Hospital, where he died Dec. 20, aged 76, of carcinoma of the lung.

Janes, Thomas Ingles, San Mateo, Calif.; Hahnemann Medical College of the Pacific, San Francisco, 1888; for many years practiced in San Francisco, where he was on the staffs of French, St. Joseph's, and Franklin hospitals; died Dec. 30, aged 90, of bronchopneumonia and cerebral arteriosclerosis.

Jolley, James Swayne ✦ Homer, Ga.; Atlanta School of Medicine, 1912; died in the Hall County Hospital, Gainesville, Dec. 7, aged 72.

Jones, Gwendolen Schlaegel ✦ New York City; Columbia University College of Physicians and Surgeons, New York City, 1929; certified by the National Board of Medical Examiners; served on the faculty of her alma mater; for many years associated with the Presbyterian Hospital; died in St. Luke's Hospital Dec. 30, aged 53.

Katz, Walter, Northport, N. Y.; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1924; specialist certified by the American Board of Radiology; veteran of World War II; since 1945 on the staff of the Veterans Administration Hospital; died in the Huntington Hospital in Huntington Jan. 6, aged 57, of pneumonia.

Keys, Richard ✦ Amarillo, Texas; Vanderbilt University School of Medicine, Nashville, Tenn., 1910; past-president and secretary of the Potter County Medical Society; associated with Northwest Texas Hospital and St. Anthony's Hospital, where he died Dec. 16, aged 74, of myocardial infarction.

Labermeier, Max Charles ✦ Cincinnati; Eclectic Medical College, Cincinnati, 1917; member of the American Academy of General Practice; member of the staff of the Jewish Hospital; died Dec. 16, aged 65.

La Mont, Charles Augustus ✦ Canton, Ohio; Johns Hopkins University School of Medicine, Baltimore, 1908; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; past-president of the Canton Academy of Medicine and the Stark County Medical Society; for many years associated with the Aultman Hospital, where he died Dec. 15, aged 76, of diabetes mellitus.

Lapierre, Jean Thomas ✦ Minneapolis; Creighton University School of Medicine, Omaha, 1924; fellow of the American College of Surgeons; on the staff of St. Mary's Hospital, where he died Dec. 25, aged 58, of cerebral embolism.

Lee, William Pulaski, Cisco, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1890; for many years city health officer; died Dec. 20, aged 95.

Loveall, George Robert ✦ San Diego, Calif; Northwestern University Medical School, Chicago, 1943; past-president of the San Diego Academy of General Practice; member of the American Academy of General Practice; veteran of World War II; on the staffs of the Scripps Memorial Hospital in La Jolla, and the Mercy and San Diego County General Hospitals; died Dec. 26, aged 41.

Lucas, Mary Suzy ✦ Erie, Pa.; Western Reserve University School of Medicine, Cleveland, 1943; member of the American Academy of General Practice; died Jan. 4, aged 40.

McClure, William Thomas ✦ Wheeling, W. Va.; University of Pittsburgh School of Medicine, 1917; veteran of World War I; served as city bacteriologist; formerly secretary-treasurer of the Association of Pathologists of West Virginia; for many years pathologist at the Wheeling Hospital; died Dec. 22, aged 68, of carcinoma of the liver and pancreas.

Machen, Francis de Sales ✦ Washington, D. C.; Georgetown University School of Medicine, Washington, D. C., 1901; served on the faculty of his alma mater; for many years chief medical examiner for the Massachusetts Mutual Life Insurance Company; died in the Washington Sanitarium and Hospital Dec. 25, aged 83, of generalized cancer and congestive cardiac failure.

Magg, Davin, Santa Ana, Calif.; Medizinische Fakultät der Universität, Vienna, Austria, 1936; veteran of World War II; specialist certified by the American Board of Radiology; served as radiologist at the Orange County General Hospital in Orange; died Nov. 29, aged 47, of a heart attack.

Manly, Frederick Wolfe, Phoenix, N. Y.; Syracuse University College of Medicine, 1897; an associate member of the American Medical Association; veteran of World War I; for many years school physician and health officer; on the staff of the Albert Lindsley Lee Memorial Hospital in Fulton; died in the Mound Park Hospital, St. Petersburg, Fla., Dec. 19, aged 88, of cancer of the lung.

Margolis, Jacob Isaac ✦ New York City; Johns Hopkins University School of Medicine, Baltimore, 1922; veteran of World War I; died in the Rockland State Hospital, Orangeburg, Oct. 20, aged 58, of chronic encephalopathy and hereditary chronic progressive chorea with mental deterioration.

Martz, Eugene Wayne, Stony Point, N. Y.; Ohio State University College of Medicine, Columbus, 1925; an associate member of the American Medical Association; for many years assistant director of the Letchworth Village Hospital in Thiells, which he joined as a research director in 1929; veteran of World War I; died Dec. 28, aged 58, of rheumatic heart disease.

Matzinger, Karl Andrews ✦ Buffalo; University of Buffalo School of Medicine, 1932; member of the American Psychiatric Association; on the staffs of the De Graff Memorial Hospital in North Tonawanda and the Buffalo General and Edward J. Meyer Memorial hospitals; died Dec. 7, aged 50, of carcinoma of the liver.

Maurer, Edward Harold ✦ Tullahoma, Tenn.; Tulane University School of Medicine, New Orleans, 1923; died in St. Thomas Hospital, Nashville, Oct. 15, aged 57.

Miessler, C. F. Otto, Crete, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1880; died in the Silver Cross Hospital, Joliet, Jan. 15, aged 98.

Mills, Robert E., Boon, Mich.; Saginaw (Mich.) Valley Medical College, 1902; died in the Mercy Hospital, Cadillac, Oct. 7, aged 82, of a cerebral vascular accident and arteriosclerosis.

Mullen, Eugene Wendell, San Jose, Calif.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1905; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; an associate member of the American Medical Association; formerly medical director and superintendent of the Agnews State Hospital in Agnew; died in the O'Connor Hospital Dec. 31, aged 79, of cerebral hemorrhage.

Ryburn, James W. ✦ Pocahontas, Ark.; Dallas (Texas) Medical College, 1903; served on the staffs of the St. Bernard's Hospital in Jonesboro and Randolph County Hospital; died Sept. 24, aged 81, of diabetes mellitus and coronary disease.

Singley, John DeVinne, Pittsburgh; University of Pennsylvania Department of Medicine, Philadelphia, 1895; an associate member of the American Medical Association; fellow of the American College of Surgeons, of which he was one of the founders; served on the staff of St. Margaret Memorial Hospital and the Pittsburgh Hospital, where he died Dec. 7, aged 87, of perforated duodenal ulcer with peritonitis.

Smith, William Carey, Goldsboro, N. C.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1936; on the staff of the Wayne County Memorial Hospital; died Dec. 10, aged 47, of cerebral hemorrhage.

Sosnovsky, Alexander, Brooklyn, N. Y.; Georgetown University School of Medicine, Washington, D. C., 1929; died Oct. 26, aged 63, of cerebral hemorrhage, hypertension, and arteriosclerosis.

Spence, Julian Almond, Saxapahaw, N. C.; Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, 1952; died in the Alamance General Hospital, Burlington, Dec. 15, aged 35, of a bleeding duodenal ulcer.

Stahl, William Martin, Sr. ✦ Danbury, Conn.; University of Maryland School of Medicine, Baltimore, 1914; fellow of the American College of Surgeons and the International College of Surgeons; veteran of World War I; past-president of the Fairfield County Medical Society; surgical consultant on the staff, and formerly pathologist, associate surgeon, and attending surgeon at the Danbury Hospital, where he died Dec. 11, aged 65, of shock and exposure to cold.

FOREIGN LETTERS

AUSTRIA

Tuberculous Epididymitis.—At the meeting of the Austrian Urological Society in November, Haschek said that tuberculous epididymitis was frequently associated with tuberculosis of the kidneys, prostate, contralateral epididymis, lungs, bones, and joints. An isolated tuberculosis of one epididymis is seen in only 50% of the cases. An epididymectomy should be performed in all patients in whom a fistula or an empyema resistant to therapy develops and in all those in whom a differentiation between benign tumor, tuberculosis, and carcinoma cannot be made. The operation is contraindicated when active tuberculosis of other organs is present. The presence of an isolated tuberculous epididymitis provides a relative indication. The decision to operate should be influenced by the response to tuberculostatic therapy, by problems of fertility, by the risk of an operation, and often by the patient's wish.

Hemolysis in Pregnancy.—At the meeting of the Austrian Society for Gynecology and Obstetrics in December, P. Elsner cited the case of a 33-year-old woman, para 2, gravida 3, who was admitted to the hospital with hemorrhage, chills, and fever. Examination showed severe hemolysis, with lesions of the liver and kidney. The patient received direct transfusions of about 4 liters of blood within 48 hours. Impending uremia was thus averted, the patient's coagulation factors were normalized, and the blood nitrogen level was decreased. Immediate and sufficient transfusion of blood is a lifesaving measure in such cases. F. Wewalka stated that patients with acute intravascular hemolysis are admitted to medical wards because of acute poisoning caused by heavy metals. Two patients with severe hemolysis and miscarriage were recently observed. Both were admitted in an advanced stage of the disease. An artificial kidney was the only possible means of dialyzing out the increasing residual blood nitrogen. Direct blood transfusions, with care taken to avoid the risk of anuria, are essential in the treatment of such patients.

Recurrent Pelvic Carcinoma.—At the same meeting, E. Schwach said that in the treatment of patients with recurrent pelvic cancer by irradiation a greater loss of the biological action of deep irradiation occurs than is generally recognized. Differences were found in the structure and demarcation of the recurrent carcinoma in the previously irradiated and in the nonirradiated tissues. Cure by irradiation is possible only in patients with shallow cancers who are treated with intratumorous or contact irradiation. Demarcated deep cancers may be successfully treated by the application of a sufficient dose of irradiation, possibly directly into or near the tumor. Care should be taken not to damage the surrounding tissue and adjacent organs, and necrotic masses should be evacuated. The recurrent tumor should be extirpated insofar as possible. An applicator with 50 mg. of radium, fastened to the closed end of a rubber tube, should then be inserted into the center of the residual tumor. The other end of the tube should protrude into the vagina. The radium is removed after about 2 days through the tube, which is left in place, and is reintroduced 10 days later. A third application may be necessary. Seven patients were treated in this way without any complications. Prolonged relief from pain and a return of the ability to walk was obtained in five patients. The recurrent carcinoma of the pelvic wall disappeared in two patients, one of whom was free from symptoms three years later.

Pelvic Irradiation.—At the same meeting, K. Weghaupt stated that all the true pelvis can be reached with effective doses of radium or roentgen rays; 1,000 to 1,200 r reaches the pelvic wall with the usual intrauterine dose of radium. About 1,000 r is given in addition to the intravaginal treatment given by radium; 2,000 to 2,500 r is effective on the parametrium or in the pelvic wall with roentgen therapy. This therapy is carried out between radium applications. It would be impossible to cure 28 to 36% of the women with carcinoma of the cervix in the third stage with this kind of treatment if the radiotherapist could not deliver a corresponding effective dose in the true pelvis. Carcinoma of the cervix rarely recurs in the true pelvis after modern irradiation therapy. In most cases a recurrent carcinoma of the pelvic wall after Wertheim's operation can be differentiated from a scar. The recurrent carcinoma may also change during the course of observation. Irradiation is, therefore, preferred to eventual operation for such recurrent carcinomas. The so-called sifting method had good palliative results in the first Gynecologic Clinic of Vienna. No permanent cure has yet been obtained. Relatively insignificant lesions of the skin may occur with this therapy. Radiogold is given intraperitoneally in addition to the regular irradiation therapy.

FINLAND

Venereal Disease.—One of the most surprising facts concerned with venereal diseases is the great difference in the behavior of syphilis and gonorrhea since the advent of antibiotics. Both diseases showed a marked fall of incidence soon after World War II, but, although syphilis is now rare, the postwar decline of the incidence of gonorrhea has not been maintained. In the last three or four years it has shown a tendency to rise rather than to fall; about 5,000 new cases must

The items in these letters are contributed by regular correspondents in the various foreign countries.

now be treated every year. In *Nordisk medicin* (vol. 56, no. 49, 1956), Dr. A. S. Härö points out that, while the incidence of gonorrhea in men over the age of 15 is now about 4 per 1,000 inhabitants, the corresponding figures for women is only 0.8. The source of the infection is discovered for only one-third of the patients. While practically all the male patients, after having detected signs of gonorrhea in themselves, seek treatment on their own initiative, only about 25% of the female patients do so. An equal percentage of women are symptom-free when first examined. Dr. Härö concluded that the seasonal changes in the incidence of gonorrhea depend largely on traveling, the seasons of the year most favorable for the contracting of gonorrhea being those in which traveling is most popular. Traveling is also an important factor in the spread of gonorrhea among seamen. Only 28% of the Finnish seamen who contract gonorrhea do so at home. The incidence of gonorrhea among seamen is about 25 times greater than that for the male population as a whole.

Reporting and Registration of Cancer.—The reporting and registering of patients with cancer was started in 1939, but World War II interrupted the measure, which was not resumed until 1953. Since then it has been in operation under the auspices of the National Cancer Association, Public Health Service, and Central Statistical Bureau. Reporting is voluntary, but practically all the main hospitals, pathology laboratories, and medical practitioners cooperate in sending reports to the registrar. Dr. E. Saxen in *Nordisk medicin* (vol. 56, no. 40, 1956) states that, while cancer of the skin is much more common in men than in women in London, there is little difference in this respect between men and women in Finland. Another curious finding in Finland concerns the high incidence of cancer of the stomach and esophagus. Cancer of the esophagus for both sexes was responsible for 3.7% of all the new cases of cancer reported, and the crude death rates were 7.5 for men and 7.9 for women per 100,000 inhabitants.

INDIA

Isoniazid Salt of Calcium Aminosalicylic Acid.—N. N. Sen (*Journal of the Indian Medical Association*, Dec. 16, 1956) used a compound of calcium aminosalicylic acid and isoniazid in 23 patients who had failed to respond to the administration, for over a year, of streptomycin, isoniazid, and aminosalicylic acid in various combinations. All of them had sputum positive for Mycobacterium tuberculosis. Each patient was given 100 mg. of the compound four times a day for 90 days. In 11 cases, the treatment had to be suspended prematurely because of the patient's intolerance to it. In the remaining 12 patients, the fever decreased in 3; the intensity of cough was diminished in 11; the quantity of sputum decreased in 8; the appetite increased in 7; there was a feeling of well-being in 11; and there was an increase in weight in 4. The sputum became negative in only one. The sedimentation rate decreased in five, but roentgenograms taken before and after treatment showed appreciable change in only one. Although the results were not very encouraging, when one considers that all these cases had proved refractory to all other antituberculosis drugs, the slight improvements shown with the new compound indicate that the drug should be given further trial for a prolonged period.

Pharmaceutical Congress.—The ninth Indian Pharmaceutical Congress was held in Calcutta in January. The executive committee of the congress formulated a Five Year Plan for the pharmaceutical industry. The congress is the first nonofficial body to make such a move.

Tuberculosis Survey.—A. N. Sen Gupta and co-workers (*J. Indian M. A.* **27**:12, 1956) reported a series of 17,516 patients studied at the outpatient clinic of the Tuberculosis Relief Association in Calcutta. The series was not a random sample of morbidity, since all the patients were suspected to be suffering from pulmonary tuberculosis. Of the total number, 8,383, or 40%, were tuberculous, including 7,214 patients with pulmonary tuberculosis. The largest number were in the age group 20 to 29 years (44%). All patients were from the low-income group. Women constituted only 27.6% of the total number of tuberculous patients, but this may be due to the smaller number of female patients attending the clinic. Intimate contact with tuberculous patients in the family seems to have played a more significant role in the lower age group than in the higher. Of the 5,969 patients with pulmonary tuberculosis whose sputum was examined, 62% showed Mycobacterium tuberculosis. Practically all types of pulmonary tuberculosis in all stages were found in the series. The largest number (90.5%) were of the infiltrative type.

Nutritional Edema.—Mehta and Gopalan (*Indian J. M. Res.* **44**:4, 1956) state that anemia is a constant feature of the syndrome of malnutrition known as kwashiorkor. A series of 18 patients with this disease was observed in Coonoor, where hookworm infestation and malaria, which complicate kwashiorkor in other parts of the world, are almost absent. The patients' ages ranged from 18 months to 5 years. The investigations included fractional gastric analysis after an alcohol meal and histamine, examination of the peripheral blood and bone marrow, estimation of plasma proteins, and examination of stools for ova of parasites. It was found that the anemia in this disease may be due to deficiency of protein, iron, or liver principle. The response to therapy was slow. In the evolution of the anemias, both deficient supply as well as defective utilization of the concerned nutrients play a part. Patients with kwashiorkor treated for a few weeks showed eosinophilia. Pronounced depression of gastric acid secretion was observed in all patients on their admission. After a high-protein diet was instituted, gastric acid secretion tended to return to normal levels.

Tuberculosis Control.—At the 14th International Tuberculosis Conference at Delhi in January, Dr. Prasad said that many health problems, including that of tuberculosis, must now be dealt with on an international level. Tuberculosis has ceased to cause dread in the patient, his family, and his neighbors. Countries with a high incidence of this disease, including India, are engaged in improving the standards of living of the people as a means of combating it. The government of India has given priority to BCG vaccination in its effort to check the disease. It was estimated that nearly 500,000 people die of tuberculosis in India every year and that 2 to 3 million suffered from it. The whole susceptible population, numbering nearly 170 million, will have been vaccinated by 1960. Already 80 million people have been tuberculin-tested and 28 million vaccinated. Three hundred clinics are being established during the current Five-Year Plan—these in addition to the 235 clinics already established.

Isoniazid-Resistant Tubercle Bacilli.—At the same meeting it was emphasized that antibacterial drugs, such as isoniazid, given alone produce resistant bacilli more quickly than when two or more drugs, for example, isoniazid and streptomycin or isoniazid and aminosalicylic acid, are used in combination. Tubercle bacilli, however, do not increase in virulence as a result of treatment with isoniazid. Dr. Walsh McDermott, of the United States, stated that isoniazid, which is cheap and effective, is useful especially in countries such as India where the number of patients is large. He pointed out that 10 patients could be treated with isoniazid alone for the same amount of money as is needed for the treatment of one patient with combined therapy. He suggested that children and young adults who are tuberculin positive or infected with tubercle bacilli should be treated with isoniazid, even though they have no outward symptoms of the disease. Dr. Sirsi, of India, pointed out that the exact mechanism of resistance and attenuation of the isoniazid-resistant bacilli is unknown. All that is known is that the drug interferes with the metabolism of the tubercle bacillus in some way.

Treatment of Pulmonary Tuberculosis in Sanatoriums.—At the same meeting many experts expressed the view that with the advent of new and efficient antibiotics treatment for pulmonary tuberculosis on an outpatient basis could be adopted to advantage, but with certain precautionary measures and with certain exceptions, as in patients who require operation. Professor Griesbach, of Germany, said that his experience showed that outpatient treatment could no longer be considered inferior to treatment in a hospital or sanatorium for all forms of pulmonary tuberculosis. The results depend not only on the type and stage of the patient's tuberculosis but also on the patient's attitude towards his surroundings, his work, and his illness. Dr. C. G. Shaver, of Canada, said that, if all inpatient services were available for home treatment, then the clinical and epidemiologic results of therapy on an outpatient basis should be as good as those for patients treated in sanatoriums. Dr. Johs Gravensen, of Denmark, said that outpatient treatment was justified if the patient was thoroughly cooperative and had undergone preliminary hospitalization early in the course of his disease and if he was kept under observation and given the benefits of operation when indicated. Dr. Howard W. Bosworth, of the United States, said that such therapy, when used properly, had become an important factor in the treatment of pulmonary tuberculosis but that the trend was definitely toward including hospital or sanatorium care whenever possible.

Antiarthritic Drugs.—Gujral and Saxena (*Indian J. M. Res.* 44:4, 1956) evaluated the antiarthritic effect of some modern drugs and a number of indigenous drugs used in the treatment of chronic arthritis by Ayurvedic practitioners. Adult male albino rats that had not undergone an adrenalectomy were used. The animals were injected in both hind feet just beneath the plantar aponeurosis with 0.1 cc. of a 2% formaldehyde solution. On the third day the same injection was repeated. Decoctions of indigenous drugs were prepared, and each drug was fed every day to a group of six rats, while another group of six served as a control. Phenylbutazone was as effective as cortisone in inhibiting the development of formalin-induced arthritis. Gold sodium thiomalate and sodium salicylate followed in that order in respect to effectiveness. The remaining drugs, both indigenous and modern, except for glycyrrhiza, failed to produce any beneficial effect.

Pectin and Streptomycin for Pulmonary Tuberculosis.—M. D. Deshmukh and co-workers (*Journal of the Indian Medical Profession*, December, 1956) state that pectin can slow down the rate at which penicillin, streptomycin, and other drugs are eliminated from the body. The elimination of streptomycin is slowed down even more than that of penicillin. Trials were, therefore, conducted to study the effects of streptomycin with pectin in rabbits and in tuberculous patients. In rabbits 50 mg. of streptomycin with pectin gave blood levels equivalent to those obtained with 100 mg. of streptomycin in distilled water. In tuberculous patients higher levels of longer duration were obtained with 0.5 Gm. of streptomycin with pectin than with 1 Gm. of streptomycin in distilled water. Biweekly use of 0.5 Gm. of streptomycin with pectin in clinical trials gave better results as regards clinical, radiologic, and general improvement than the biweekly use of 1 Gm. of streptomycin alone. In both groups, isoniazid was also used in daily dosages of 200 mg. As pectin is inexpensive and nontoxic, its use in combination with streptomycin will greatly reduce the cost of treatment. Even in acute cases in which 1 Gm. of streptomycin a day is indicated, use of 0.5 Gm. of streptomycin with pectin would maintain an equally satisfactory blood level. In less acute cases, 0.5 Gm. of streptomycin with pectin given every third day would maintain a satisfactory blood level of streptomycin.

Creatinine Clearance Test.—S. C. Agarwal (*Indian J. M. Res.* 44:4, 1956) stated that the blood urea clearance test often fails to give an accurate picture of renal function. He therefore investigated the suitability of the endogenous creatinine clearance test. Four-hourly endogenous creatinine clearance values were preferred to 24-hour clearance values. The test was performed on 40 healthy men 19 to 47 years of age who had no history of renal disease. The variability of the test appeared to be much less than that of the urea clearance test. Therefore, it seems to be superior to the latter in assessing renal function. The extent of renal impairment should, however, be calculated in relation to the generally lower endogenous creatinine clearance value obtained in Indian subjects.

Treatment of Choleric Uremia.—H. N. Chatterjee (*Antiseptic*, January, 1957) stated that uremia is the second most fatal complication of the cholera syndrome, ranking next only to circulatory failure. The extrarenal causative factors are severe shock; great loss of fluid; extreme capillary dilatation in internal organs, including the kidney; and intravascular hemolysis of blood. The acute kidney failure is of an almost specific type, and the clinical manifestations are completely reversible. These facts and the presence of extreme capillary dilatation led the author to give antihistamines intramuscularly to 20 patients in the treatment of uremia during the cholera epidemic of 1954. The antihistamines used were pyrilamine maleate (Anthisan), chlorpromazine hydrochloride, and promethazine hydrochloride. All the patients had cholera and a history of anuria of five hours' or more duration. Twenty patients used as controls were treated in the same way, except that the injections they received contained no antihistamines. Only about half of the patients had positive stool cultures. Pyrilamine failed to relieve the anuria in 3 of 11 and chlorpromazine in 2 of 11 patients with positive stool cultures. Promethazine failed in 1 of 17 patients. In the control group there was complete anuria in 4 of 16 patients with positive stool cultures. The average time for starting urination after the last injection was 12 hours for pyrilamine, 10 hours for chlorpromazine, and 9 hours for promethazine. In the control group this interval was 24 hours after starting usual treatment with saline solution.

Pyrilamine showed no special advantage over the treatment given the control group so far as the cure rate was concerned. Chlorpromazine possessed the disadvantage of causing a dangerous depression of blood pressure. Promethazine seemed to be of definite help as regards both decreasing mortality and prompting the earlier onset of urination; there were no untoward reactions. The cholera epidemic of 1955 was unusually severe. In this epidemic a combination of promethazine and vitamin C was used as part of the treatment and as a prophylactic against uremia. Any patient in whom urination did not occur within two hours after the administration of saline solution was given promethazine intramuscularly. Urination was thus established in 80%. Patients who did not so respond within a further period of eight hours were given 500 mg. of vitamin C intravenously. In a few patients both drugs had to be given every 12 hours. There were no deaths from uremia in the author's series of 227 consecutive cases. In the peak month (May), the case fatality rate was 5% in contrast to the general cholera mortality of 32% for Calcutta as a whole. The average time required to reestablish urination after the administration of promethazine was eight hours.

ISRAEL

Erythrocyte Abnormality.—Periodic disease is not rare in Israel. It is characterized by recurrent attacks of abdominal pain with muscular rigidity and high fever and sometimes pleural and joint pains. A high sedimentation rate and often leukocytosis are found. It is preponderant among people of Mediterranean origin but occurs, although more rarely, among Ashkenazi Jews. A. de Vries and co-workers report in *Harefuah* (52:4, 1957) on some hematological and serologic findings in 12 patients with periodic disease, 3 of Ashkenazi and 9 of Mediterranean origin. Spherocytes were found in the smears of all patients. Ghost cells were prepared from erythrocytes by gradually decreasing the osmotic pressure of a dialyzing medium. The membrane of normal erythrocytes treated in this way has a granular aspect when observed in the electron microscope. Electron micrographs of ghost cells obtained from erythrocytes of patients with periodic disease showed two abnormalities: the membrane was thinner than normal and it was smooth and agranular. These abnormalities were found in 8 of the 12 patients; in one, all the ghosts were thin and smooth, while in the other 7, only some of the cells showed this characteristic. The abnormality was also found in some patients who were in a state of remission.

The antibody response in the patient's serum agglutinating normal erythrocytes (type O) treated with papain was also found to be different in patients suffering from periodic disease. While 150 normal serums did not agglutinate papainized normal erythrocytes (type O), the serum of 7 of the 12 patients with periodic disease caused agglutination in titers from 1:1 to 1:16. The agglutinin is of the warm antibody type. It is not a hemolysin, and it is not destroyed during 30 minutes' incubation at 56 C. Of the eight patients on whom microscopic, electron microscopic, and serologic studies were performed, five showed all three abnormalities. In some, however, the agglutinin was found in serums collected at periods other than those at which the morphologic observations were made. In one patient, all three findings were positive on several occasions; in others, at certain dates, the electron micrograph was positive while the serum was negative for antibody. In some of the patients' relatives, spherocytes and agglutinin for papainized normal erythrocytes (type O) were found. Some of them had never had clinical manifestations of periodic disease.

Native Dermatitis.—An occupational dermatitis was described by Shanon and Sagher (*Harefuah* **51**:275, 1956). The disease appears from July to October. All the affected persons were engaged in handling prickly pears. The dermatitis has a striking similarity to scabies, and the condition of a number of the patients was previously so diagnosed. The lesions were vesicles and papules 2 to 5 mm. in diameter. Pustules appeared, probably as a result of secondary infection after scratching. Occasionally small areas of superficial ulceration were present. The covered parts of the body were secondarily affected by self-transfer or transfer to others of broken-off bristles (glochidia) from the primarily affected sites. The disease is hardly mentioned in the medical literature: there are a number of publications that refer to the trauma caused by the thorns of the cactus tree but not of the fruit. Therapeutic measures are directed toward extracting the glochidia. This is sometimes impossible because of the attached barbs that point toward the base of the bristle. Soothing ointments relieve the subjective symptoms and keratolytic ointments are used in order to bring about quicker desquamation. Prophylaxis is directed to avoidance of contact between the fruit and the skin. The histological picture revealed the bristles in the epidermis and cutis. Individual cell keratinization of the prickle cells was found in the epidermal pustules. It is not known whether the mechanical trauma or the contents of the bristles cause these changes.

Need to Expand Medical Faculty.—A demand to expand the Hebrew University–Hadassah Medical Faculty in Jerusalem so as to be able to graduate 150 physicians every year was voiced by E. Kanev, chairman of the Kupath Holim Center, at a meeting of the Public Health Medical Council in Tel-Aviv. The last census revealed that there are only 3,259 physicians and 583 dentists in the country. If the number of physicians no longer practicing directly is deducted, there is one physician for every 600 residents. Moreover, 55% of the physicians are over 55 years old and may be expected to retire from active practice within the next 15 years. Hence the country is faced with a potential shortage of physicians.

NORWAY

Labyrinthine Damage from Tuberculous Meningitis.—During the period 1948 to 1954, inclusive, 55 patients with tuberculous meningitis were admitted to the Ullevaal Hospital. Of the 32 patients who survived, 26 participated in a follow-up study of their cochlear and vestibular function. Hearing was tested by pure-tone audiometry and vestibular function by the caloric test. Only 12 of the 26 patients had normal hearing. Twelve of the 14 patients with impaired hearing had received dihydrostreptomycin alone, and many of them had been given compartively large doses. Impaired hearing due to dihydrostreptomycin was observed in most of these patients only after a dosage exceeding 175 gm. in adults and about 45 gm. in children. Impaired hearing due to streptomycin, on the other hand, was not demonstrated. In his report in the *Journal of the Oslo City Hospitals* for November, 1956, Dr. Jens G. Hall points out that the incidence of impaired hearing after dihydrostreptomycin treatment is so high that the use of this drug is hardly justifiable. He also notes that impairment of hearing is a far worse handicap than a vertigo, to which the patient will ultimately be able to adjust. Although streptomycin is held by some to be more toxic to the vestibular apparatus than dihydrostreptomycin, the present investigation suggests that the incidence of vestibular damage is much the same for the two drugs. Both these antibiotics should be replaced, if possible, by drugs not producing the above-mentioned side-effects.

Venereal Disease.—In *Nordisk medicin* for Dec. 6, 1956, Dr. H. C. Gjessing draws attention to the success with which the public health authorities have handled the administration of penicillin. Any physician needing it for the treatment of a patient with venereal disease may secure a free supply, but he must fill in an application form for each patient. In so doing, he is encouraged to remember to report his cases to the health department. The patient receiving treatment in a public hospital does not have to pay for it, but if he fails to appear on being summoned for reexamination the police may demand an explanation of his nonappearance. The law does not, however, provide any penalty for such nonappearance.

SWEDEN

A Census of the Medical Profession.—In May, 1954, as the first step in an inquiry into the activities of physicians, some 200 physicians in Malmö were requested to fill out a series of questionnaires. These were so elaborate that their recipients on filling them in had an opportunity to give valuable information about their activities. The physicians were classified into the following main groups: (1) those who did nothing, (2) those who had some occupation other than medical, (3) those in private practice, (4) those who were district medical officers, (5) those who were municipal medical officers, (6) those who were the head of a hospital, and (7) those who held a subordinate hospital appointment. Classifications 8 and 9 were miscellaneous in composition. The data supplied showed the relative numerical significance of these different groups, their geographical importance, the character of the services rendered, the time spent on them, and plans for the future. Since the preliminary trial had worked out satisfactorily, the next step was taken in November, 1954, when the questionnaires were addressed to every one of the 5,553 members of the medical profession in Sweden. Failure to fill in the forms was due to death, illness, traveling abroad, and various other factors; however, more than 92% sent in a reply (*Svenska läkartidningen*, Dec. 7, 1956). Among the main conclusions to be drawn from this census are

the following: About 20% of the Swedish medical profession is engaged in private practice, and 88% are members of the Swedish Medical Association, this percentage being as high as 98 for members in responsible positions. About 50% hold subordinate hospital positions; here the number of women is comparatively large. The mean age of assistant hospital physicians is 36 years; this means that junior hospital appointments are often held by the middle-aged. A growing number of Swedish physicians practice for more than three years before settling down to some definite medical activity, and about 50% of the hospital physicians plan to remain in hospital service for 10 years or more.

Frequency of Overweight.—In the spring of 1954 the Swedish Red Cross Society started a comprehensive campaign for a census of blood donors for hospital services. Taking advantage of this campaign, Dr. Bertil Sjövall measured the heights and weights of the prospective donors. The 3,500 men and 4,000 women in his series can be taken as a fairly representative sample of the community, except that men in military service, persons exempted from civil defense because of illness or other reasons, and persons in the higher age groups were not included. Guided by the tables of the Metropolitan Life Insurance Company, Sjövall, whose report is published in *Svenska läkartidningen* for Dec. 21, found that from the age of 40 up more than 50% of all the persons examined were overweight. Of the women over 40, 20% were found to be 20% or more overweight. The weight rose rather steadily with age. Among women, overweight was more common in those in rural than in urban areas. Overweight was more common among the married than among the unmarried women, but there was no difference in regard to whether the women had or had not borne children. A classification of the men according to the four social classes failed to show any marked differences in the incidence of overweight based on this factor.

UNITED KINGDOM

Centenary of British Medical Journal.—The *British Medical Journal* celebrated its centenary on Jan. 3, 1957. It first appeared under that title on Jan. 3, 1857, before which time it was known as the *Association Medical Journal*. The change of name followed the establishment of the British Medical Association. The new name was agreed on at the annual meeting of the Provincial Medical and Surgical Association in York in 1855, but the final change of title was not effected until Jan. 3, 1857.

Death After Insulin.—Death from overdosage with insulin given for the shock treatment of mental disease is rare. The Manchester city coroner recently recorded a verdict of death from misadventure at an inquest of a woman who died in the hospital after an injection of insulin had been given to her by her family physician for the treatment of a mental condition. The coroner said not only that the wrong type of insulin had been administered but also that it should not have been given by a general practitioner for this particular purpose. However, he thought that the physician acted with the best of intentions, under the circumstances. The woman died in the hospital from bronchopneumonia secondary to hypoglycemic coma. The physician stated that he was called in by the patient's husband because of her mental condition, which was beyond control. The physician tried to get her into a mental hospital but, since all beds were full, was unable to do so. He therefore attempted to induce in her an insulin coma. She went into the coma and never recovered consciousness. Death occurred 12 days later.

Traffic Accidents.—Traffic accidents were increasing in Great Britain until gasoline rationing began on Dec. 17. Although between 4,000 and 5,000 people are killed in such accidents annually and 10 times as many are seriously injured, it is perhaps not appreciated that about as many people commit suicide, more are killed in accidents in the home, and 4 times as many die from cancer of the lung. Data are being collected on the cause and extent of injuries incurred in accidents; on experimentally caused accidents involving dummies; and on the use of protective devices in automobiles. The risk of death from compression of the chest by impact against the steering wheel can be lessened by padding the hub to distribute the force of impact or by using a wheel that projects several inches above the hub so that on impact the supports of the wheel are bent. Padding of the dashboard with foam plastic reduces the severity of injuries to the head, face, and knee. Crash helmets are protective but unlikely to be used by motorists. The use of a safety belt to prevent striking the head against the body of the car as well as of improved locks to stop the doors from flying open at the time of the collision is suggested.

Venereal Disease.—The Council of the British Medical Association has authorized an inquiry in certain areas into the extent to which venereal disease is now being treated outside hospitals. The number of new cases seen at hospital clinics has fallen sharply, and the council is of the opinion that this might represent an apparent rather than a real decrease in the incidence of venereal disease. The simplicity of treatment with penicillin may have led many patients to seek treatment outside the hospital. General practitioners and consultants in the areas selected for the investigation will be asked to fill in a questionnaire on the number of patients they treated in 1956 without reference to a venereologist. The names of neither the patients nor the physicians treating them will be disclosed in any report on the survey.

Monopolies on Oxygen and Medical Gases.—An investigation by the Monopolies and Restrictive Practices Commission reveals that oxygen is a monopoly of the British Oxygen Company, which, in addition to controlling about 98% of the oxygen used in Great Britain, also holds agencies for the supply of most of the plant and equipment used in its manufacture. The commission emphasized that a heavy responsibility falls on

the company to supply all the oxygen needed by industry, the armed forces, and hospitals. In the opinion of the commission, the company does not carry out sufficient original research on new processes for the production and distribution of oxygen, most of which were discovered abroad, with the company being content to acquire the necessary patent rights or licenses to enable them to be exploited here. Rapid technical progress is still being made, but mainly in the United States and Germany. Industrial oxygen is produced for $3.65 per 1,000 cu. ft. (28 cu. m.). Although industrial oxygen more than meets the standard of purity required by the British Pharmacopoeia, medical oxygen costs $10.25 per 1,000 cu. ft., or nearly three times as much. This is an excessive price to pay for smaller cylinders and a day and night delivery service. There are no published prices, and some hospitals within the same management group are paying different prices for their oxygen. The company records shows an average loss of 11% on cost for medical oxygen, and there seems to be no justification for any losses sustained on the sales of medical oxygen being carried by industrial consumers. The commission also objects to the company's trading under different subsidiary names without revealing the fact to prospective purchasers. It concludes that the charges of the British Oxygen Company for oxygen are unjustifiably high.

Expectation of Life.—In his quarterly report the registrar general of England and Wales stated that in 1955 the expectation of life of males at birth was 67.52 years and of females 72.99. The comparable figures based on the mortality rates of 1953 to 1955 were 67.46 and 72.86 respectively.

Hypotensive Drugs and Renal Function.—The renal hemodynamics in patients with hypertension treated with hypotensive drugs have been investigated by McDonald and Goldberg (*Lancet* 1:77, 1957). They measured the renal plasma flow, glomerular filtration rate, filtration fraction, renal vascular resistance, and cardiac output in patients with severe hypertension before and during treatment with pentolinium tartrate and reserpine. Apart from changes in renal vascular resistance, little alteration in the renal hemodynamic pattern was noted. The urinary excretion of sodium fell. There was a slight reduction in the glomerular filtration rate and filtration fraction in those patients in whom the blood pressure fell, but this was considered of no significance except in those patients suffering from severe renal impairment before treatment, since the condition of these patients may deteriorate during treatment with hypotensive drugs. The authors state that periodic determinations of blood urea level afford a good guide to the progress and management of patients with hypertension treated with hypotensive drugs.

Abrahams and Wilson carried out similar studies on hypertensive patients suffering from chronic renal disease and impaired renal function (*Lancet* 1:68, 1957). They found that the effect on renal function depended largely on the initial degree of renal impairment and partly on the type of renal disease. Usually patients with chronic type 1 nephritis, pyelonephritis, and malignant hypertension showed no deterioration of renal function when the initial creatinine clearance value was over 50% and the blood urea level was below 60 mg. per 100 ml. Renal failure progressed when the initial creatinine clearance value was below 30% and the blood urea level was above 70 mg. per 100 ml. In chronic type 2 nephritis the results of hypotensive therapy were disappointing, and it was found to be of no value in delaying the onset of renal failure. There was no evidence that the lowering of blood pressure accelerated the deterioration in renal function, although this possibility could not be excluded. Adequate control of blood pressure seemed to prevent the malignant hypertensive termination in renal disease, although it did not prevent cerebral vascular accidents. Most patients were relieved of headache, distressing dyspnea, and visual disturbances, and for this reason alone Abrahams and Wilson consider that treatment with hypotensive drugs is justified.

Fatty Acids and Blood Cholesterol.—It has been suggested that the effects of dietary fat on the serum cholesterol level in man, which is thought to be related to atherosclerosis, depend on the degree of unsaturation of their constituent fatty acids. Fats containing the "essential" unsaturated fatty acids, such as linoleic acid, have been thought to produce lower serum cholesterol levels than those containing saturated acids, such as stearic acid. The former are present in vegetable fats, the latter in animal fats. To test these views, Keys and co-workers have examined the serum total and β-lipoprotein cholesterol levels in controlled experiments on 26 men in caloric balance on a diet constant in all respects except for the character of test fats (*Lancet* 1:68, 1957). The test fats were corn oil, sunflower seed oil, sardine oil, and butterfat, all of which were given in quantities of 100 gm. daily. Other mixed food fats in the diet amounted to 40 gm. daily, and total fats represented 39.8% of the total calories. The mean serum total cholesterol levels were 216.9 mg. per 100 ml.; on the butterfat diet, 181.1 mg. per 100 ml.; on sunflower seed oil, 181.1 mg. per 100 ml.; on sardine oil, 177.1 mg. per 100 ml.; and on corn oil, 164.9 mg. per 100 ml. Thus corn oil produces the lowest serum cholesterol level. These figures are not in the order of the degree of unsaturation of the fats or of their linoleic acid content. Corn oil is less saturated and contains less linoleic acid than sunflower seed oil.

The findings of Keys and co-workers do not support the view that the serum cholesterol level in man is a simple inverse function of the essential fatty-acid content or of the degree of unsaturation of the fatty acids in the diet. Their view is that populations increase the fat content of their diets by consuming more saturated and unsaturated fats, although the increase in the latter is smaller. According to the authors, the serum cholesterol level is directly related to the total consumption of fat rather than inversely related to the consumption of essential or highly unsaturated fatty acids.

CORRESPONDENCE

HUNGARIAN REFUGEES IN AUSTRIA

To the Editor:—Several physicians who responded to my appeals, which were published in THE JOURNAL, Dec. 22, 1956, page 1568, have requested me to write, telling of our progress in according direct aid to refugee Hungarian doctors in Austria. Our Hungarian relief crusade continues apace and, although the oppressive emergency has abated, the insistent need for aid continues. When I wrote last, 218 refugee doctors had registered with us. As of this date, 677 have applied to us for help.

We have found by experience that the best and most direct way to help our Hungarian colleagues is to accord them $20 upon arrival, $10 for every week they remain in Austria, and $3 per day for board and lodging for those colleagues who have been designated to private quarters. We allot $1.00 per day for each additional member of the doctor's family. There are no organizational or administrative expenses deducted. Every penny received is utilized for direct aid for our refugee Hungarian colleagues.

My appeals, which you published, evoked a heartwarming response—not so much in numbers but in the quality of the kind words and good wishes we received. In all we received 286 checks from individual physicians and from a few medical societies. In every instance, each contribution was immediately and thankfully acknowledged. We are particularly thankful to the International College of Surgeons, the American Medical Association, and the Medical Society of the State of New York for having sent us $1,000, $5,000, and $5,000 respectively.

We regret that space limitations prevent our listing the names of the societies and physicians who have sent us their personal contributions. We avail ourselves of this opportunity to thank them each for their generosity. Our committee has particularly requested that I mention Mrs. Peter G. Denker, the wife of a New York City physician, who has aided us immeasurably. Mrs. Denker, on her own initiative, has instigated a campaign for our cause that has accounted for a considerable number of contributions.

Our surveys reveal that approximately 450 refugee physicians desire to remain in Austria attending that time when they can safely return to their practice in Hungary. We are, whenever possible, urging them to remain in Europe, for we feel that many of these colleagues would, should they emigrate to the United States, experience difficulty with language and "state board" requirements. To maintain them here, however, will require our further support for many months to come.

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RETREAT FOR THE BUSY PHYSICIAN

To the Editor:—The states of Utah, Colorado, New Mexico, and Arizona meet at an ill-defined area called the Four Corners. This vast, beautiful but desolate land of rocky mountains and sage-covered sand is the home of the Navaho Indians. Bluff, Utah, is a tiny settlement of 18 houses. Two miles from here up the San Juan River is St. Christopher's mission to the Navaho—a cluster of one-story rock and adobe buildings in the style of the early western missions of some hundred years ago. Here Father Liebler and other workers, both clerical and lay, of the Episcopal Church minister to the Navahoes. Here they give state-approved schooling for the children, medical care in their year-old 12-bed hospital, and government surplus food such as eggs, butter, and milk. For the past several years I have flown into this isolated community on monthly trips with various other doctors. I was unable to obtain air transportation after last winter. Since the summer of 1956 a prominent eastern physician has lived and worked there not only to do good for these poor people but to get away from a busy practice to a place of isolation where he might do work under different surroundings and have an opportunity to think. He will return to his home and his practice this spring refreshed in spirit and in body. He will have a new outlook on life, a different philisophy by which to live, and memories of having performed a fine work. It occurs to me that there must be many physicians—surgeons, general practitioners, gynecologists, etc.—who may wish to "get away from it all" for three months or more. There must be physicians, too, with the missionary-medico spirit who always wanted to work as Dr. Albert Schweitzer in Central Africa but will never be able to realize their ambition. Here is an opportunity to perform a great medical mission to our own primitives in a wildly primitive part of our country while our income taxes are spent abroad for the betterment of other primitives.

For the physician who would like to do this work in return for food and lodging and for the spiritual rewards that only he would seek but who would like to maintain contact with his fellow doctors, there are Salt Lake specialists who are willing to travel to Bluff to confer with him. There is also the college of medicine in Salt Lake City with its School of Post Graduate Studies, where the physician may journey for short courses or which will send him audiovisual kits or books and journals from the medical library. Interested physicians may write to me for more information.

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MISCELLANY

THE DOCTOR IN RUSSIA

Following are excerpts from the article "The Soviet Doctor's Dilemma" by Mark G. Field, reproduced with permission from Problems of Communism, *January-February, 1957.*—ED.

Evidence supports the contention that, quantitatively, medical services available to the people of the Soviet Union have improved enormously. The number of hospital beds rose from 176,000 in 1913 to 247,000 in 1928; 791,000 in 1940; 1,011,000 in 1950; and 1,290,000 at the end of 1955. There were about 24,000 doctors in Russia before the Revolution; the official figure for 1955 is 334,000.

Under the Soviet system, however, the expansion of medical institutions has been accompanied by the creation of a large bureaucratic apparatus to administer them and to keep the physician under state control. This has in turn affected medical organization, redefined the role and social position of the physician, and introduced certain non-medical elements into the patient-physician relationship. Contrary to the expectations raised by official propaganda, the Soviet patient encounters all kinds of deficiencies and shortages in medical care, bureaucratic inefficiency and indifference, physicians who act more like policemen than doctors, overcrowded facilities, and often the lack of the most common medicine.

Such shortcomings exist mainly in the medical service available to the ordinary citizen. Medical care, like other components of the Soviet living standard, is differentiated according to social position and official rank, and the higher the rank the better the service.

"Class" Distinctions in Medical Care

Basically there are two types of medical "networks": the general and the closed or restricted network. The general network is maintained by the Ministry of Health or by industrial organizations (under the Ministry's supervision), and its function is to dispense Soviet "socialized medicine" to the mass of ordinary Soviet citizens. Medical services in the general network are of poorer standard than those available in the restricted network, particularly in rural areas and on the collective farms.

Within the restricted system there are two classes of medical facilities. The first serves the employees of certain administrations. There are, for example, medical networks reserved respectively for Army and Navy personnel, for the lower-echelon workers of the Ministry of Internal Affairs, and for railroad workers. These organizations maintain their own separate hospitals, polyclinics and rest homes. In the larger cities the difference between these facilities and those provided by the general network may be slight. In the smaller towns and rural areas, however, the facilities in a "closed" clinic of this type probably are substantially superior to those available to the ordinary public.

The second type of closed network, and the one on which the least amount of information is available, consists of the medical installations reserved for the top stratum of party, government and administrative officials. When a Soviet citizen refers to a "closed polyclinic" (*zakritaia poliklinika*) he usually means a clinic reserved for the "big shots." Within this category there is, again, a whole gradation depending on rank, extending up to the very apex of the official pyramid. Even within the Kremlin walls medical care and hospitalization are divided into well-defined categories; the higher the rank of the patient the better, of course, the facilities and the more individual attention he gets from the doctors. At this level the quality of medical care compares with the best available in the West.

Below the system of Kremlin polyclinics and rest homes there are, in every major town, closed facilities reserved for the local party and government elite. In small localities, where the number of high officials does not warrant a special building, a part of the existing medical facilities may be set aside for them. There everything from the physicians to the attending personnel, furniture, and food is better than in the "ordinary" wing. Medical care in the closed network is also provided by the state at no cost to the patient.

Position and Prestige of the Doctor

Generally speaking, the position and prestige of the medical profession is somewhat lower than that of most other professions. *The Soviet hero is not the healer but the man who builds machinery for industry or the one who fights for the cause.* And, by the same token, the financial rewards which doctors can command compare unfavorably (with certain exceptions) with those of government officials or skilled industrial workers.

In the course of a recent trip to the Soviet Union, this author was struck by the low salaries ordinary physicians received as compared to the salaries of the people they treated. For example, during a visit to the Kharkov Electro-Mechanical Plant I was told that most qualified workers earned approximately 2000 rubles a month. The physician at the plant's *Zdraypunkt* (dispensary), however, stated that he earned only about 900 rubles. The average physician's salary was reported to be about 750 rubles to 800 rubles a month.

The doctor is also at a relative disadvantage vis-à vis other members of the intelligentsia when it comes to obtaining housing and furnishings. Housing, for example, is assigned first to party and other officials, then to technical and other specialists: only what is left over is available to physicians. This incongruity between the importance of the doctor's function and the reward he receives is probably the deterrent that turns many talented young people away from medicine. It is interesting to note in this connection that *in the Soviet Union medicine has become a woman's occupation:*

about seven to eight out of ten doctors are women. whereas before the Revolution the figure was less than one in ten. On the other hand, there is evidence that most of the top jobs in Soviet medicine are held by men rather than women.

Of equal sociological interest is the fact that there is no such thing as an independent association of physicians. Since the Soviet regime feared that autonomous professional associations would constitute independent loci of power, all pre-revolutionary medical associations were declared illegal on the ground that they were "counterrevolutionary." They were replaced by a nationwide structure, the Union of Medical Workers, through which the regime maintains strict control over physicians, dictating in minute detail methods of work and procedures to be followed.

The Union has also been used as a political weapon through which members of the medical profession can be accused of malpractice with complete immunity on the part of the regime.

Control Over Medical Work

In order to assert and maintain their operational control over the medical profession, the regime and the bureaucratic organizations that employ physicians must perforce standardize the doctor's work. One aspect of such standardization is the imposition of precise time norms upon the physician. While the doctor in private practice in an unregimented society budgets his time according to his professional standards and case load, under the Soviet bureaucratic system time allocation appears to be done *by* the bureaucracy *for* the physician. In a sense *patients cease being the physician's patients and become the system's patients.* The bureaucracy determines how the collective time of *its* physicians will be distributed among its patients. A time norm is allocated to each doctor, and he must perform his services within this limit. The Ministry of Health, for example, has established that a physician working in a dispensory *must see not less than six patients per hour and should spend no more than ten minutes with each patient.* Norms vary slightly with different specialties: surgeons must examine ten patients per hour; clinicians, gynecologists and obstetricians six (seven in the out-patient department); otolaryngologists, eight; dentists, two. One house call is considered the equivalent of three office visits.

It will be noted that almost half of the average of 8.15 minutes spent by the doctors with each patient was consumed by paper work exclusive of the reading and writing of the case histories.

A brief review of the mechanics of granting sick leaves will show precisely how the physician's role is integrated into the system of labor controls. A worker who is sick is entitled to part payment of his salary prorated according to the length of his employment at his current job. The plant trade union organization administers this payment, but only after the worker presents an official "bulletin" issued and signed by a physician in his official capacity on the staff of a plant clinic or neighborhood dispensary. Bulletins signed by a private physician or by a "paying" polyclinic have no validity in this respect. The bulletin itself is numbered, one copy remaining at the clinic while another is given to the patient. When the latter reports back to work, he gives his copy to the attendance checker, who notes on it the type of work done by the worker and the number of days absent from work. After the foreman verifies this data, the bulletin is sent to the clinic, where the physician in charge of the particular shop of the patient checks it, registers it, and sends it on to the personnel department. There the worker's labor book is examined and the length of uninterrupted work at the plant is noted. The bulletin then goes to the shop social insurance commission's chairman, who verifies the bulletin and enters on the individual's union record the fact that he has received one. Only then, and only if the commission's decision has been favorable, can the payroll department begin its calculation of the compensation due.

It can be presumed that trade union inspectors, as well as doctors employed by the trade union for this purpose, constantly watch the curve of absenteeism caused by illness and that a physician who consistently grants more sick leaves than his colleagues will have some explaining to do.

The physician is strictly limited also in the number of days of sick leave he can prescribe for a patient. Usually he can grant three days' leave and renew the certificate twice for equal periods, but no physician alone has the authority to grant more than ten days. The patient who requires further leave is referred to a Consultative Medical Commission (*Vrachebnaia Konsultativnaia Kommissia*, or VKK) which determines (1) whether the doctor was justified in excusing the patient in the first place, and (2) what should be done with the patient, i.e., should he be returned to work, kept under observation, or hospitalized. If the disability is considered permanent, the patient is sent to the Medical Commission for Determining Work [Capacity] (*Vrachebnaia Trudovaia Expertiznaia Kommissia*, or VTEK), which is under the Ministry of Social Security and which determines degrees of disability and amount of pension.

When physicians are law in evaluating claims for medical excuses, the authorities may impose such norms as temperature minima to automatically sift "sick" from "healthy" patients in disregard of the fact that many illnesses are not accompanied by a rise or fall in body temperature. Or the physician may be limited to an absolute quota—i.e., a percentage of the total individuals assigned to him—in granting sickness excuses over a stated period of time. To go beyond this figure would be to court trouble.

The Doctor's Dilemma

That there is a continuing conflict between the physician's humanitarian impulses and the role the regime expects him to play is clearly revealed in the Soviet press. Doctors frequently are condemned for excessive goodness of heart, gullibility, indifference or irresponsibility.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

The Problem of Arrhythmias in Cardiac Emergencies. I. F. Tullis. J. Kentucky M. A. **55**:37-42 (Jan.) 1957 [Louisville].

Tullis reports on 6 men between the ages of 44 and 66 years in whom clinical emergencies were produced by arrhythmias. Paroxysmal atrial tachycardia occurred in the 1st patient, whose coronary reserve was probably impaired, and the combination precipitated a clinical picture of a mild cardiac emergency. The patient, however, was able to cooperate, and the primary nature of the tachycardia was immediately evident. Ventricular tachycardia occurred in the 2nd patient, who presented findings resembling those in myocardial infarction, with marked circulatory collapse. Physical examination did not show the primary problem of a heart rate of 200 beats per minute. Emergency electrocardiography established the diagnosis of ventricular tachycardia and changed the treatment plan to one of interrupting a serious arrhythmia instead of treating a fresh myocardial infarction. The 3rd patient had no significant impairment from his rheumatic mitral valvular disease until atrial fibrillation suddenly appeared. This led in rapid sequence to congestive heart failure, probable occurrence of a small embolism in the aortic bifurcation, and a paralyzing left carotid embolism not significantly improved by embolectomy. The 4th patient had a posterior myocardial infarction that was seriously complicated first by a complete atrioventricular block and a ventricular rate of 33. Then the clinical picture was complicated by ventricular tachycardia, which at least in part was most likely precipitated by the use of levarterenol (Levophed) bitartrate to maintain the blood pressure. The patient was given procainamide (Pronestyl) hydrochloride intravenously and quinidine gluconate intramuscularly, followed by quinidine sulfate orally. He also received potassium chloride and dextrose in water, and the tachycardia suddenly stopped. The cardiac mechanism reverted to sinus rhythm after a period of 2nd degree heart block, and the patient made an uneventful recovery. Atrial flutter alone produced clinical findings strongly suggestive of myocardial infarction in the 5th patient. The use of quinidine was instrumental in causing full-blown ventricular tachycardia. Intravenous administration of digitalis, although after procainamide hydrochloride was given, seemed to produce the most beneficial effect and the rhythm reverted to normal sinus mechanism. The 6th patient had an acute anterior myocardial infarction aggravated by a complete atrioventricular block with a slow idioventricular rate and periods of asystole. The management of the atrioventricular block successfully increased the ventricular rate and by so doing elevated the blood pressure, but the patient died of the extensive infarction.

There are circumstances in which an ectopic rhythm becomes the primary factor producing a cardiovascular crisis, and there are other cases in which ectopic rhythms, which would otherwise not be alarming, produce serious problems by complicating myocardial infarction, congestive heart failure, or cardiovascular therapy. These rhythms include chiefly atrial tachycardia, atrial flutter, atrial fibrillation, ventricular tachycardia, and complete atrioventricular block. Appropriate circumstances include elderly persons with latent coronary insufficiency, patients with known coronary insufficiency, and patients with other forms of organic heart disease. Such attacks may be characterized by chest pain with dyspnea, pallor, sweating, weakness, or collapse; shock; acute pulmonary edema; acute congestive heart failure; or Stokes-Adams attacks with fainting, loss of consciousness, or generalized convulsions. After identification of the arrhythmia and assessment of its contribution to the findings, the physician should have immediately in mind the initial treatment he will administer in a given situation.

Teeth, Streptococcus Viridans, and Subacute Bacterial Endocarditis. F. G. Hobson and B. E. Juel-Jensen. Brit. M. J. **2**:1501-1505 (Dec. 29) 1956 [London].

Streptococcus viridans was the causative agent in 43 of 59 patients with subacute bacterial endocarditis who were admitted to the Radcliffe Infirmary in Oxford, England. None of the 43 patients was edentulous. The diagnosis was confirmed by a positive blood culture in 25 (58%); the diagnosis rested on the clinical picture in 18 patients (42%), but was confirmed by autopsy in 5. The initial attack of subacute bacterial endocarditis was specifically related to dental extraction in 7 patients (16%) who underwent teeth extractions 10 to 42 days before admission to the hospital. Relapses of subacute bacterial endocarditis occurred in 5 (20%) of the 25 patients with a positive blood culture of Str. viridans who had retained some teeth after the initial attack of subacute bacterial endocarditis had been subdued. Such teeth as they retained had been evaluated as "good" after clinical and radiological examination in 4 patients; the teeth that were considered "bad" had been removed under antibiotic cover during the initial attack of subacute bac-

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The place of publication of the periodicals appears in brackets preceding each abstract.

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terial endocarditis. Dental extractions were not carried out in the 5th patient until the second relapse of subacute bacterial endocarditis. The antibiotic cover consisted of the administration of 8 million to 12 million units of soluble penicillin daily, given at four-to-six-hour intervals. Three patients yielded a positive blood culture of Str. viridans after the dental extraction, although this bacteremia was immediately controlled. Six patients yielded a very heavy growth of Str. viridans within 12 hours from teeth, both "bad" and "good," that were extracted under a similar antibiotic cover. Antibiotic cover for dental extractions in patients in the course of active therapy thus did not prevent a bacteremic shower, although this was immediately controlled, nor was this antibiotic cover effective in sterilizing the tooth sockets or mucous membranes of the mouth.

The small series of patients reported on can be regarded as representative of the patients with subacute bacterial endocarditis admitted to any large general hospital. The evidence overwhelmingly incriminates the teeth as the all-important source of infection in patients with subacute bacterial endocarditis caused by Str. viridans. A formidable, but preventable, hazard is ever present in the lives of these patients so long as teeth or fragments of teeth remain in their jaws. Scrupulous complete dental clearance should be carried out as an essential step of the therapeutic attack on the disease in all patients with subacute bacterial endocarditis caused by Str. viridans.

A Clinical Evaluation of the C-Reactive Protein Test. R. S. Yocum and A. A. Doerner. A. M. A. Arch. Int. Med. **99**:74-81 (Jan.) 1957 [Chicago].

One thousand two hundred sixty-two C-reactive protein tests were performed with the serum obtained from 729 patients admitted to the U. S. Public Health Service Hospital in San Francisco. One hundred sixty-three of the 729 patients had infectious disease, 213 had gastrointestinal disease including metabolic disturbances, 127 had disease of the cardiovascular system, 53 had collagen disease and other diseases of sensitivity, 34 had neoplastic disease, 12 had hematological disease, and 127 had miscellaneous diseases. The C-reactive protein was consistently found in the serums of patients with bacterial infections, acute rheumatic fever, acute myocardial infarction, and widespread malignant processes. It was commonly, but not consistently, found in the serums of patients with rheumatoid arthritis, virus infection, and active tuberculosis. The reaction of the patient's serum to the test was rarely found positive in limited primary carcinoma with no clinical evidence of metastases.

The C-reactive protein has been reported by other workers to appear as an acute phase-response in a variety of conditions, such as trauma, infections, necrosis, neoplasms, and granuloma formations. Any positive test is considered abnormal and should stimulate further investigative studies to determine the causative factor. The C-reactive protein test proved to be more accurate than the erythrocyte sedimentation rate in the presence of inflammatory or necrotic processes. The C-reactive protein test proved to be more sensitive than the erythrocyte sedimentation rate; it often was positive before the erythrocyte sedimentation rate increased and often became negative before the erythrocyte sedimentation rate was restored to a normal level. Patients with some diseases had positive results from the C-reactive protein test originally, and in them the test was considered a useful guide as to the presence or absence of activity and correlated well with the clinical course in most instances. This observation may be useful in following patients on steroid therapy. The test is an extremely simple, useful procedure that readily lends itself to routine office or hospital practice.

Role of Coronary Sclerosis in Hypertensive Cardiopathy. A. C. Taquini. Medicina **16**:69-86 (April) 1956 (In Spanish) [Buenos Aires].

The incidence of clinical symptoms of coronary sclerosis was investigated in a group of 1,706 patients with essential hypertension that was benign in 1,364 patients, malignant in 158, associated with diabetes in 96, and renal in 88. In the groups with either benign hypertension or hypertension associated with diabetes, most of the patients were women over 50 years of age, the blood pressure was below 220/120 mm. Hg, and the eyeground changes were mostly of group 2 in the Keith-Wagner-Barker classification. In the groups with either malignant or renal hypertension, most of the patients were under 50, the blood pressure was above 220/120 mm. Hg, and the eyeground changes were mostly of groups 3 or 4. The incidence of symptoms of coronary sclerosis was 22% for patients with benign hypertension, 7.6% for those with malignant hypertension, 32% for those with diabetes, and 4.5% for those with renal hypertension. There was no relation between the blood pressure level on the one hand and the degree of cardiac hypertrophy on the other, and the incidence of symptoms of coronary sclerosis. Heart failure occurred more frequently in patients with either malignant or renal hypertension than in those with benign hypertension or diabetes, but symptoms of coronary sclerosis did not appear in any patient with heart failure who also had malignant or renal hypertension. Symptoms of coronary sclerosis were associated with heart failure in 80% of the patients with benign hypertension or diabetes. The results of the investigation show that hypertensive heart disease in patients with malignant or renal hypertension is independent of coronary sclerosis and the result of hypertension per se.

Cor Pulmonale in Patients with Emphysema. H. J. Sluiter and N. G. M. Orie. Wien. Ztschr. inn. Med. **37**:437-445 (Nov.) 1956 (In German) [Vienna].

In a series of 56 patients with emphysema, 49 had a history of bronchial infection, 46 had a history of asthma and/or hay fever, and 28 had bronchiectasis. Cardiac decompensation occurred in 22 of the 56 patients and right ventricular hypertrophy was revealed by the electrocardiogram in 14 of the 22 patients.

Mechanical factors do not, as a rule, produce decompensation of the right side of the heart in patients with emphysema. Functional disturbances, and particularly hypoxia, play a much more important part in the causation of insufficiency of the right side of the heart. Such a hypoxia does not occur, or only in a very mild degree, in patients with uncomplicated emphysema, and hypoxia does not depend on the severity of the emphysema. The extent of the hypoxia depends on the severity and the extent of the chronic pulmonary infections and of the superimposed acute pulmonary infections. It is the hypoxia (or hypercapnia) that causes pulmonary hypertension. The reversible infections that cause the decompensation explain the fact that the roentgenogram and the electrocardiogram often do not reveal an abnormal condition of the heart except during the phase of decompensation. The sudden occurrence of decompensation thus also finds its explanation. With a relatively small burden placed on the heart, the pulmonary infections likewise cause the insufficiency of the right side of the heart. Coronary sclerosis, pulmonary fibrosis, and asthmatic factors definitely contribute to the causation of decompensation, but they may rarely cause decompensation by themselves. Chronic bronchial infection is responsible for the frequent absence of polyglobulism despite continued hypoxia.

Treatment consisted of administration of antibiotics to combat the infections; administration of spasmolytic drugs, aminophylline, sympathomimetics, and cortisone to combat asthma; and administration of oxygen and digitalis. None of the 22 patients, who went through 28 phases of decompensation, died in the course of decompensation.

A Simple New Procedure for Diagnosis of Bronchogenic Carcinoma: Comparison with Known Methods. I. S. Epstein, M. G. Sevag and F. E. Brown. Cancer **9**:1075-1084 (Nov.-Dec.) 1956 [Philadelphia].

The content of blood-free solids was determined in aspirates of bronchial secretion obtained from 110 patients, of whom 54 had malignant lung tumors and 56 had noncancerous pulmonary lesions. The arithmetic mean percentage of blood-free solids was 5.5% for the patients with cancerous lesions and 2.59% for those with noncancerous lesions. This difference is highly significant. A tentative dividing point of 4% was selected for further tests of the method. Of the 54 patients with cancerous lesions, 45 were correctly classified positive; 53 of the 56 patients with noncancerous lesions were correctly classified as negative. This is a total of 89.1% (98 of 110) correct classifications. These results were compared with those obtained by Papanicolaou's test, bronchoscopic findings, and x-ray findings. All diagnostic methods gave the same results in 58 of the 110 patients. Interpretation of the chest roentgenogram correctly identified 19 of 20 patients with cancerous lesions, but it also classified the lesions as cancerous in 26 of 31 patients with noncancerous lesions. The bronchoscopic report had the poorest record of the 4 techniques for both groups of patients; it classified only 8 of 20 cancerous lesions as positive and incorrectly identified as cancerous 10 of 31 noncancerous lesions. The determination of percentage of blood-free solid identified correctly 11 of 21 cancerous lesions and classified only 3 of 31 noncancerous lesions incorrectly. The Papanicolaou test gave about the same results, with correct classification of 12 of 21 cancerous lesions and incorrect classification of 5 of 31 noncancerous lesions.

The new technique compares favorably with the 3 other diagnostic methods used in this study. Neither the new method nor any of the 3 others gives perfect reliability, but the new method has higher discriminating powers than either the chest roentgenogram or the bronchoscopic report. The Papanicolaou test and the new technique seem to have about equal discriminatory powers.

Studies on the Effect of a Low Lipid Diet and Lipotropic Agents in Cerebral Atherosclerosis. G. Lindqvist and B. Isaksson. Acta med. scandinav. **156**:109-120 (No. 2) 1956 (In English) [Stockholm].

Seventeen hospitalized patients between the ages of 50 and 87 years with cerebral atherosclerosis who had more or less marked mental symptoms, persisting disturbances in motility after cerebral thrombosis, or paralysis agitans were treated with a lipid diet for 11 weeks. The diet contained 25 gm. of fat and less than 75 mg. of cholesterol per day. Ten of the patients were given a mixture of 0.75 gm. of choline chloride, 0.75 gm. of betaine chloride, and 0.25 gm. of inositol three times daily. Determination of the serum lipids was performed at the beginning of the therapeutic trial and after 5 and 11 weeks. All samples were taken in the morning on an empty stomach. Determinations were made of total lipids, total and free cholesterol, and total phospholipids and their subfractions, i. e., lecithin, kephalin, and sphingomyelin. The patients underwent a clinical examination of the mental state, motility, and condition of the heart and eyegrounds before the beginning of the therapeutic trial and after 11 weeks. Three patients were discharged after 5 weeks because of unexpected improvement; their control examination took place at the time of the discharge.

Eleven of the 17 patients showed evidently nonspecific improvement of the mental condition, which also led to improvement of the motility in 8 whose ability to benefit from physical and occupational therapy was increased. A significant decrease of the total serum cholesterol content was observed in 10 of the 11 patients who had an initial content above 200 mg. per 100 cc. This effect was somewhat more pronounced, at least at the end of the treatment period, in the group that had been given lipotropic agents. The lecithin and the nonlecithin phospholipid fractions did not present concordant changes. The nonlecithin phospholipid fraction generally decreased in both groups of patients, but the lecithin fraction generally was unchanged or increased. The total cholesterol-lecithin ratio decreased in most patients, especially in those who were given lipotropic agents. There was no correlation between the clinical results and the changes in

the serum lipids. Studies on the influence of a low lipid diet on the total lipids seem to be of little value because of the greatly varying changes that occur in the various lipid fractions. No method for the direct determination of the neutral fat fraction is available. Calculation of neutral fat is of limited value because it involves several sources of error,such as admixture of water and salts.

Hormone Treatment of Malacic or Porotic Osteopathy: Etiological and Therapeutic Considerations. L. Barbera. Riforma med. **70**:1319-1330 (Nov. 17) 1956 (In Italian) [Naples, Italy].

Parenteral administration of hormone had a beneficial effect on 6 patients with malacic or porotic osteopathy. Each patient received 200 rat units of hormone every day for 15 days and then every other day for 15 additional days. The treatment was suspended for from 2 to 3 months as soon as clinical improvement and attenuation of the pain were evident. The same dose of hormone was then given again every other day for 20 to 30 days. Remission of pain was the main effect of the treatment. Ambulation without help was possible 30 days after the beginning of the treatment. The hormone had a beneficial effect on the general nutrition and that of bones and muscles. The serum inorganic phosphorus level increased in all patients, especially in those with osteomalacia. The increase of phosphatase was constant and marked. The level of blood calcium tended to decrease. Cholesteremia diminished in 4 patients and increased in 2. The basal metabolic rate decreased constantly in all patients. The body weight, the appetite, and the hematologic findings improved in all patients. Roentgenologic examination did not show much improvement, but in 1 patient all spontaneous fractures were healed and the calcium content of the bone became normal.

Q Fever—Human Aspects. A. L. Craddock. East African M. J. **33**:435-440 (Nov.) 1956 [Nairobi, East Africa].

Thirteen cases of Q fever were observed in 10 male and 3 female Europeans between the ages of 9 and 47 years in Nakuru, Kenya. The disease was characterized by a sudden onset with chills, and, during the course of the illness, by flushed skin, sweating, intense headache, anorexia, and nausea. Some of the patients showed evidence of segmental pneumonia. The clinical diagnosis of Q fever was confirmed in 9 patients by laboratory findings; the rickettsial complement-fixation test gave a positive result with Coxiella burnetti antigen in a titer of 1:100 or over. Complement-fixation tests with other rickettsial antigens gave negative results. The clinical features of the remaining 4 patients suggested a diagnosis of Q fever, but the titer of the complement-fixation test was below the accepted diagnostic titer of 1:100; the diagnosis, therefore, was not regarded as being confirmed.

Nakuru is surrounded by an extensive dairy farming area in which the sources of human infection with C. burnetti (cattle, sheep, and goats) are numerous. These animals excrete the organism in the urine, feces, milk, placenta, and fetal membranes, so that patients may be infected either by drinking milk or by inhaling dust, in which the organism is remarkedly persistent. Q fever is endemic in Kenya. The patients' response to chlortetracycline was dramatic. An initial dose of 0.5 gm. followed by administration of 0.25 gm. at 8-hour intervals, with a total dose of 4 gm., usually proved adequate. Chloramphenicol was also effective, but the response to this antibiotic was slower. Chlortetracycline is the drug of choice.

Portal Hypertension as Assessed by Hepatic Venule Catheterization. G. E. Welch, G. E. Malaret, C. C. Craighead and others. South. M. J. **50**:6-7 (Jan.) 1957 [Birmingham, Ala.]

Occlusive catheterization of the hepatic venule is a valid means of assessing portal pressure. The authors used this method in 19 patients. Ascertained by this technique, the normal hepatic venule pressure ranges from 12 to 22 cm. of isotonic sodium chloride solution, but in a group of patients with portal hypertension the pressure in the hepatic venule ranged from 27 to 34 cm. Simultaneous observations of pressure in the hepatic venule and portal vein were made in 10 subjects, and the coefficient of correlation between the 2 pressure sites was found to be 0.87 ± 0.77. Assessing the portal pressure may aid in the location of the site of either intrahepatic or extrahepatic portal obstruction. The forced Valsalva manuever produces a rise of 60 to 70 cm. of isotonic sodium chloride solution in normal subjects and in patients with liver disease. The selection of patients for portacaval shunt may be facilitated, since there is a small group that may have ascites, relatively good liver function, and no hemorrhage and may benefit from the shunt procedure provided significant portal hypertension is present. This technique of catheterization of the hepatic venule to determine the pressure in the portal system can be used not only to predict the success or failure of portacaval shunt operations but also to follow patients postoperatively to ascertain the patency of the shunt.

Acute Thrombosis of the Portal Vein. E. L. Posey, J. W. Long and S. L. Stephenson. South. M. J. **50**:8-16 (Jan.) 1957 [Birmingham, Ala.].

Acute thrombotic occlusion of the portal vein is a comparatively uncommon disorder and is generally regarded as fatal. A survey of autopsy reports from the Mississippi Baptist Hospital and the Veterans Administration hospital of Jackson revealed an incidence of 0.42%. The disorder appears nearly twice as frequently in males as in females, probably because of the higher incidence among men of hepatic cirrhosis, the most common etiological factor. Hepatic cirrhosis and intra-abdominal malignancy are the 2 most common causes of thrombosis of the portal vein. The picture of acute thrombosis of the portal vein is usually superimposed upon some preexisting pathological process. For this reason, the classic manifestations rarely appear in a "pure" form.

The following symptoms appear in various combinations: Pain is moderate to severe, sudden in onset, and steady or colicky in nature. The distress is felt in the right upper quadrant or epigastrium and is frequently referred to the back. Gallbladder colic may be mimicked exactly. Nausea and vomiting are common. Ascites may be obvious or may be discovered only at laparotomy or postmortem examination. Ascites does not appear in all patients, particularly not in those with efficient collateral circulations. Other symptoms are splenomegaly of minimal to moderate degree, diarrhea, melena, ileus, hematemesis, shock, and terminal coma. Once gastrointestinal thrombosis develops, the course is relentlessly downhill to death. Death comes not from the portal vein thrombosis per se, nor from interruption of portal blood flow, but from the complications arising from propagation of the clot, usually intestinal thrombosis. Even if the condition responsible for thrombus formation is a potentially fatal disorder, by prevention of these complications life can at least be prolonged; should the cause be benign, life can be saved. Anticoagulant therapy, preferably with heparin, begun early in the course of the disease, offers a logical means of preventing these complications. A case is presented illustrating the successful results of heparin therapy. The patient is in excellent health 2 years after recovery.

Specific Resistance to Bovine Insulin. H. H. Kreutzer, J. J. Moors and R. Verhille. Nederl. tijdschr. geneesk. **100**:3598-3610 (Dec. 8) 1956 (In Dutch) [Haarlem, Netherlands].

A 59-year-old woman came to the clinic because of symptoms of mild rheumatoid arthritis. Examination revealed that she also had diabetes mellitus. At first the diabetes was controlled by diet alone. The joint pains responded to treatment with calcium salicylate. The patient did not strictly adhere to her diet, nor did she come regularly for control tests of her diabetic status. Several months later her 24-hour urine was found to contain 100 gm. of sugar, and the fasting blood sugar content was 186 mg. per 100 cc. At first she refused insulin injections, but later she consented, and she was given protamine-zinc insulin (a bovine insulin). At a control examination several months later, acetonuria was found and she was hospitalized. Her blood sugar content was 331 mg. per 100 cc., the urine contained 7% sugar, and acetone was present. Dietetic measures were instituted, and she was given injections of ordinary insulin, in 3 daily doses of 40, 30, and 30 units. Despite these measures the fasting blood sugar level remained high, and when the evening injection of ordinary insulin was replaced by protamine-zinc insulin there was no reduction in the fasting blood sugar level. The resistance to insulin increased to such an extent that the daily requirement was 2,000 units.

When hog insulin was tried, however, the daily requirement was only 60 units. Return to bovine insulin, even in large doses, was accompanied by high blood sugar values and glycosuria, whereas a smaller dose of hog insulin reduced the blood sugar level and rendered the urine free of sugar. Various brands of insulin had the same effect. Insulin-tolerance tests proved bovine insulin to be ineffective, whereas hog insulin was effective. Tests on guinea pigs revealed that the patient's serum contained substances that neutralized bovine insulin to a great extent but hog insulin only slightly or not at all. Hemagglutination tests yielded a postive result with bovine insulin in a serum dilution of 1:320, whereas the result was negative with hog insulin in a dilution of 1:10. Such resistance to insulin derived from a particular animal species suggests that in some patients insulin resistance may be due to the development of antibodies.

SURGERY

Hemodynamic Study in the Course of Operation of Persistent Ductus Arteriosus. G. O. Oustrières, P. Vernant and J. Mathey. Rév. franç. études clin. et biol. **1**:1105-1120 (Dec.) 1956 [Paris].

Pulmonary artery pressures were measured during operative closure of the ductus arteriosus in 41 patients between the ages of 6 weeks and 20 years. Most of them were nursing infants. Persistent ductus arteriosus was the only abnormality in 38 patients. The authors divided the patients into 3 groups, according to hemodynamic changes in response to the closure of the ductus arteriosus: 1. Fifteen patients were without pulmonary artery hypertension, i. e., with less than 30/15 mm. Hg. The closure of the ductus arteriosus caused no alteration of pressure. 2. Twenty-one patients had moderate pulmonary artery hypertension (from 30/15 to 50/30 mm. Hg). The closure caused immediate return to normal pressure. High pressure was observed in only 1 patient with a reversed shunt. Pulmonary artery hypertension appeared to be associated only with increased pulmonary blood flow. 3. Ten patients had pulmonary artery hypertension of more than 50/30 mm. Hg. The closure was associated with both an increased blood flow and increased peripheral resistance in the pulmonary circulation. A left auricular hypertension with well-marked V waves was found in all patients with an increased pulmonary blood flow. This auricular hypertension after closure of the ductus arteriosus is analogous to the pulmonary artery pressure.

Surgical Treatment for Aneurysms of the Aortic Sinuses with Aorticoatrial Fistula: Experimental and Clinical Study. J. L. Sawyers, J. E. Adams and H. W. Scott Jr. Surgery **41**:26-42 (Jan.) 1957 [St. Louis].

The rupture of an aneurysm of an aortic sinus of Valsalva into the right atrium results in an aorticoatrial fistula. The illustrative case presented concerned a 32-year-old surgeon who had been healthy and active until July, 1954, when, after climbing a steep hill, he became dyspneic and had to sit down to rest. Although there was no precordial pain, palpitation caused him some anxiety. He recovered after a few minutes' rest and since this time has remained essentially asymptomatic except for occasional episodes of palpitation. A few weeks later, on a routine examination, his physi-

cian, who had followed him closely for many years, noted a cardiac murmur. No murmur had existed previously. There was a continuous, high-pitched, whistling murmur audible over the entire precordium and maximal in intensity in the 4th and 5th right intercostal spaces close to the sternum. Fluoroscopy revealed prominence of the pulmonary vascular markings with increased pulsations of hilar vessels and moderate enlargement of the right atrium and of the right ventricle. Cardiac catheterization revealed evidence of a large left-to-right shunt at the level of the right atrium. On the basis of the history and findings on physical and laboratory examination, the diagnosis was rupture of a congenital aneurysm of an aortic sinus of Valsalva into the right atrium with the establishment of an aorticoatrial fistula. During the 2 years since the episode of acute dyspnea, the patient has remained essentially asymptomatic. He has avoided strenuous activity but has carried on an active surgical practice and has played golf regularly. The murmur has persisted and there has been no increase in heart size.

In order to obtain data concerning the pathological characteristics and clinical behavior of congenital aneurysms of the aortic sinuses of Valsalva, the authors reviewed all 47 cases they were able to find in the literature since Thurman's first description in 1840. The nature of the lesion was confirmed at autopsy in 45 of these cases, while in 2 patients who are still alive the diagnosis rests on clinical grounds with substantiation by catheterization studies. Syphilitic and mycotic aneurysms were not included in this review. Among the 45 cases confirmed at autopsy, a total of 49 aneurysms of the aortic sinuses were encountered. Rupture of the aneurysm had occurred in 37 of the 45 patients seen at autopsy. A suture anastomosis between the right atrial appendage and ascending aorta will produce an aorticoatrial fistula. Such a suture anatomosis was made in 14 dogs, and cardiac catheterization studies were made before and after this operation. It was found that experimental aorticoatrial fistulas of 3 to 4 mm. in diameter are fairly well tolerated for many weeks to months, while fistulas of 5 to 10 mm. in diameter between the aorta and the right atrium result in death from cardiac failure within a few days in most instances. In recent years, there have been a few attempts to close aorticoatrial fistulas in patients. Four such efforts, in each of which a slightly different method was used, have come to the attention of these authors. None of the methods has been successful, and each patient died at or after operation. Autopsy reports and experimental studies indicate that this intracardiac lesion should be repaired under direct vision by carefully placed sutures.

Subtotal Pericardectomy for Constrictive Pericarditis. W. G. Bigelow, F. G. Dolan, D. R. Wilson and R. W. Gunton. Surgery 41:102-111 (Jan.) 1957 [St. Louis].

The results obtained in 10 patients subjected to pericardectomy at the Toronto General Hospital between 1939 and 1950 are briefly reviewed. The authors suggest that operative failures and recurrences may be due to myocardial atrophy or inadequate excision of pericardium. They present a preliminary report of 13 subtotal pericardectomies with results based on a 1-to-3-year follow-up. All 13 patients were placed on the usual strict cardiac regimen preoperatively with digitalis, diet, and diuretics until their condition was considered optimum and their weight steady and minimal. A transternal incision allows wide excision or subtotal pericardectomy with the greatest safety. There is no advantage in the midsternal incision, since it would be impossible to adequately resect the pericardium without entering both pleural cavities. The important thing in a transternal incision is that opening or spreading the wound occurs principally by virtue of the upward movement of the superior segment. The inferior wound edge is relatively stationary. Thus, the incision should be placed over the lowest area to be exposed. The 4th space on the right and 5th space on the left have been found satisfactory in most cases. A V-shaped cut is made across the sternum to aid in accurate realignment of the wound. The sternum has solidly united in all cases. The pericardium overlying the anterior and diaphragmatic surface of the ventricle is excised together with the left lateral surface of the heart after freeing and retracting the phrenic nerve. On the left side, the tip of the left auricle is usually exposed and the left pulmonary vein freed. Usual care is taken in the region of the anterior descending branch of the left coronary and the atrioventricular groove. Dissection is usually not carried up on the great vessels but is extended to free the superior and inferior venae cavae. The removal of the pericardium from the body of the right atrium is only carried out if this can be done with ease. The left pulmonary vein is also freed in the region of the lung root.

There was 1 operative and 1 postoperative death, and on the basis of a follow-up of 1 to 3 years, there has been no recurrence of symptoms in the 11 survivors. One of the 11 survivors was operated on too recently for proper assessment. The remaining 10 have been assessed as having 7 excellent, 2 very good, and 1 fair result. The latter patient is gradually improving. The authors emphasize that this is a preliminary report, and no conclusions may be drawn from this number of cases. Clinical results and hemodynamic studies so far suggest that adequate excision of the pericardium is an important factor in success.

Spontaneous Rupture of the Oesophagus: Diagnosis and Successful Management. A. Clain and S. J. Heffernan. Lancet 2:1284-1286 (Dec. 22) 1956 [London].

Spontaneous rupture of the esophagus is much more common in men than in women. There were 86 males in 100 published cases. The condition should be suspected if a middle-aged or elderly man presents with intense upper abdominal or lower chest pain that has begun after vomiting. The pain is very severe and is unrelieved by morphine. It is due to mediastinitis. In typical cases a triad of physical signs may be detected; tachypnea, abdominal rigidity, and emphysema in the neck. Rupture of the esophagus may be misdiagnosed as perforated peptic ulcer, and in many fatal published cases fruitless laparotomy has been

done. A straight x-ray film of the chest and upper part of the abdomen should be taken. In spontaneous perforation of the esophagus either mediastinal emphysema or a pleural effusion will be noted, whereas with a perforated peptic ulcer these features will be absent. The picture of rupture of the esophagus may also simulate severe coronary thrombosis, but electrocardiography shouuld clarify the diagnosis. A dissecting aneurysm of the abdominal aorta should be differentiated by the presence of a pulsatile mass in the abdomen, with absent, or unequal, femoral pulses. A case is presented in which the clinical features were so typical that rupture of the esophagus was suspected before the operation.

Surgical treatment offers the only hope for the victim of this catastrophe and should be attempted in every instance through either a thoracic or an abdominothoracic approach. If the patient's condition permits, the tear should be sutured. A large drainage tube should be placed to the site of the tear in every case, irrespective of whether suture has been possible, and attached to an underwater drainage apparatus. On the other hand, if the diagnosis has been at fault and a laparotomy has been done, the occasion is one for boldness, because the patient is doomed if surgical treatment is not attempted. It is permissible to introduce an aspirating needle into the left pleural cavity for diagnosis through a lower rib space in the anterior axillary line and also through the diaphragm via the peritoneal cavity. The laparotomy incision should be converted into a thoracotomy by extending it through the costal margin and resecting either the 7th or the 8th rib as in total gastrectomy and in esophagectomy. This operative approach is facilitated if a sandbag is placed under the left lower ribs posteriorly, and it is an even greater advantage if a table that tilts laterally is available.

The Surgical Excision of Psoas Abscesses Resulting from Spinal Tuberculosis. J. A. Weinberg. J. Bone & Joint Surg. **39A**:17-27 (Jan.) 1957 [Boston].

Eleven men and 2 women between the ages of 27 and 61 years with psoas abscesses arising from tuberculous lesions of the spine were operated on. Eight of the 13 lesions extended along the psoas major, reaching the lesser trochanter of the femur or extending beyond it into Hunter's canal. The tract of 3 lesions extended along the iliacus, and the 2 remaining abscesses were bilateral with extension to either the lumbar or femoral triangle. Almost all of the tracts showed constrictions and irregular branchings, and they varied from narrow sinus tracts to large sacs with a capacity of more than a liter. Nine patients had draining sinuses. Bony and cartilaginous sequestrums were found in 8 of the 13 patients. The surgical procedure consisted of the extirpation of the abscess together with the bony and cartilaginous sequestrums, which were either free in the tract or lodged in the diseased vertebral bodies. The operation was performed with the aid of general anesthesia. A solution containing 1 gm. of streptomycin and 500,000 units of penicillin in 20 cc. was instilled in the wound. One gram of streptomycin daily intramuscularly and 100 mg. of isoniazid orally 3 times daily or 4 gm. of aminosalicylic acid orally 3 times daily were given for 2 weeks before and for 2 weeks after the operation. After that, streptomycin was given twice a week while the dose of the other drugs remained unchanged. Antibiotic therapy was usually continued for 6 months. Complete bed rest was maintained for at least 6 months postoperatively, preferably with the patient in a body cast.

There have been no deaths. The only serious operative complication was complete severance of the femoral nerve during dissection of the pelvic portion of a sinus tract. The portion of the nerve between the psoas and iliacus was obscured by inflammation in this patient. The severance was recognized at once because of the accompanying forceful jerk of the thigh. Immediate repair was followed by complete return of function to the quadriceps femoris. The operation resulted in the arrest of the disease in all but 1 patient, in whom the sac was incompletely removed. All of the patients gained weight and showed the general improvement in health expected after the removal of an empyematic sac. Several patients became gainfully employed for the first time in years. These results gain significance when it is realized that all were adults in whom the disease was firmly entrenched and that many had had draining sinuses for months or years. Ten of the 13 patients had been treated previously with streptomycin combined with isoniazid or aminosalicylic acid or both, without favorable response. Four of the patients had firm fusion of the vertebrae of the involved region as a result of a previous operation, indicating that the suppurative lesion had progressed in the presence of a solid ankylosis. In view of the failure of previous therapy it would appear that excision of the abscess was the necessary additional factor needed to arrest the disease. Long-term results cannot be predicted, but the favorable response in these patients, who were observed for variable periods of up to 6½ years, establishes the practical value of this procedure, which is designed to heal psoas abscesses or sinuses resulting from tuberculous caries of the spine.

The Results of Combined Drug Therapy and Early Fusion in Bone Tuberculosis. A. R. Allen and A. W. Stevenson. J. Bone & Joint Surg. **39A**:32-42 (Jan.) 1957 [Boston].

Seven men, 5 women, and 5 children between the ages of 1 and 52 years with bone tuberculosis were treated at the Central Washington Tuberculosis Hospital. Thirteen of the 17 patients had associated pulmonary or renal tuberculosis. Six had draining sinuses. All 17 were given combined treatment with streptomycin, aminosalicylic acid, and isoniazid for 72 days. The patients then were operated on. Fusion of the spine was done in 12 patients, fusion of the hip in 1, fusion of the knee in 3, and saucerization in 1, who had cystic tuberculosis of the fibula. The average duration of hospitalization was 237 days. Chemotherapy was continued, if indicated, until 6 months after operation. Fusion seemed to be safe, even in the presence of

draining sinuses, after an average of 72 days of chemotherapy. There were 15 successful fusions resulting from the first operation. The patients were followed up over a period of 12 to 40 months. All patients returned to their previous occupations regardless of the amount of physical activity involved. Of the specimens cultured from the patients with extrapulmonary tuberculosis, 80% were positive despite chemotherapy. Chemotherapy was less effective in sterilizing extrapulmonary disease than in the treatment of pulmonary tuberculosis.

A Clinical Evaluation of Tendon Transplantation in the Paralytic Foot. L. R. Straub, J. P. Harvey and C. E. Fuerst. J. Bone & Joint Surg. **39A**:1-16 (Jan.) 1957 [Boston].

A follow-up study was carried out in 181 paralytic or deformed feet in which a total of 214 tendons were transferred singly or in combination in 164 patients. One hundred thirty-three of the 164 patients had residua of poliomyelitis with distinct variation in deformity and involvement, such as valgus deformity in 40 feet, varus deformity in 11 feet, and calcaneus deformity in 12 feet. Hyperextension and cock-up of great toe had resulted from paralysis of the tibialis anterior muscle in 75 feet. Recurrent congenital clubfoot was present in 25 feet and miscellaneous conditions in 12 feet; 6 feet belonged to patients with cerebral palsy. Tendon transfers were done in most patients in the 1st and 2nd decades of life. Tendons were inserted by 3 different methods, i.e., by intraosseous suture or the implantation of the tendon into a bed or channel of bone with suture of the tendon to bone and to periosteum; by the loop method, that is, passage of the tendon end through an osseous tunnel and back to be sutured to itself; or by Bunnell's method, with a pull-out wire passed through a hole in the bone of insertion, the wire being tied over a button on the sole of the foot. The results did not seem to be appreciably affected by any of the 3 methods used. Satisfactory results were obtained in 142 feet and unsatisfactory in 39 feet. It was found to be impossible to evaluate the degree of tension under which a tendon was attached, but it seems that a maximum degree of tension is desirable for the best result. Some transfers failed when they had to function against a fixed deformity of bone. An opposite deformity was produced by a tendon transfer in only 1 foot. The strength of those tendons that had been passed subcutaneously rather than beneath the inferior extensor retinaculum was impressive in certain feet, especially in clubfeet. Results of the operations done in the 1st decade of life did not differ much from those of operations done in the 2nd.

The benefits derived from tendon transfer arise from the removal of a deforming factor almost as often as from the application of a positive force in a new site. Stabilization of the foot by triple arthrodesis was carried out 74 times. Triple arthrodesis in a good weight-bearing position was important in the outcome of the average tendon transfer. The tibialis anterior muscle, when normal, provides a more functional transfer than the other muscles about the ankle. This was most noticable in the patients with clubfoot but was also true of the group with residua of poliomyelitis. Transfers to the heel for calcaneus deformity resulting from poliomyelitis proved worthwhile. For the most part, a satisfactory result requires osseous stabilization. Failure was often due to tendon laxity at the time of the operation or to the pulling-out of the tendon attachment in the postoperative period. Ten clubfeet, however, had excellent results from tendon transplants when the attachment was by intraosseous suture. This is not a particularly strong suture method, and yet the outcome was good. Rating of the tibialis anterior tendon in patients with clubfoot dropped only 0.6 of one degree after transfer. The tibialis anterior function after transfer backward through the interosseous membrane was better than that of the tibialis posterior when it was transferred forward. The reason for this is not apparent.

End Results of Focal Débridement in Bone and Joint Tuberculosis and Its Indications. E. Kondo and K. Yamada. J. Bone & Joint Surg. **39A**:27-31 (Jan.) 1957 [Boston].

Eight hundred thirty patients with 914 lesions of bone and joint tuberculosis were treated at the orthopedic clinic of the University Medical School in Kyoto, Japan, and were followed up for periods of from 1 to 21 years. End-results may be considered fully significant only after at least 5 years. The average follow-up period in these patients was 9.2 years. Of the 914 lesions, 598 were of the trunk (spinal and pelvic caries) and 316 were of the extremities. Two hundred sixty-two lesions were treated with streptomycin and 652 without it. End-results of treatment in lesions of the trunk were inferior to those in lesions of the extremities, and the results of treatment with streptomycin were superior to those obtained without streptomycin. The results of conservative treatment with and without streptomycin were compared with those of spinal fusion (Albee's operation) with and without streptomycin and with those of focal débridement with and without streptomycin in the patients with spinal caries. Except for the reduction in death rate, there were no pronounced differences between the results of conservative treatment with and without streptomycin and between the results of spinal fusion with and without streptomycin. Spinal fusion was not definitely superior to conservative treatment. The results obtained with focal débridement with streptomycin in spinal caries were definitely superior to those of any other treatment used, and almost the same results were obtained in the treatment of pelvic caries. Comparison of the results of conservative treatment with and without streptomycin in tuberculosis of the extremities with those of focal débridement with and without streptomycin showed that the results of focal débridement with streptomycin were definitely superior to all the other forms of treatment. Focal débridement in a major joint consisted of removal of all loose cartilaginous fragments, loose devitalized bone fragments, ob-

viously devitalized abscess materials, and as much of the abscess wall as possible. Focal débridement in the spine consisted of the removal of all sloughed-off cartilaginous disk remnants, loose bone fragments, and the evacuation of the abscess contents, but the abscess wall was not removed.

The use of antituberculous drugs in the treatment of bone and joint tuberculosis has a definitely favorable effect, but the maximum effect is obtained if they are combined with radical focal débridement. Focal débridement combined with streptomycin is the method of choice. The superiority of this operation can be definitely proved after the operation by the rate of healing of sinuses or abscesses, by the course of the sedimentation rate, and by roentgenograms. Firm bony ankylosis resulted from focal débridement after 1 to 2 years in most patients. Arthrodesis may better be performed secondarily, when needed, and focal débridement primarily.

Experimental Research on Surgery of the "Bloodless" Heart: Local Hypothermia of the Heart Combined with General Hypothermia. D. Melina and C. Pollara. Minerva chir. 11:923-929 (Oct. 15) 1956 (In Italian) [Turin, Italy].

The authors report on the results obtained in 14 dogs subjected to operation under general hypothermia of 26 to 28 C and local cardiac hypothermia of 20 C. Local circulation of the heart was arrested for periods up to 45 minutes. Eight dogs survived the operation. In order to assure the best results the local cardiac hypothermia of 20 C should be induced in as short a time as possible. Ventricular fibrillation did not occur while the circulation of the heart was arrested. The type of operation performed had no effect on the return of normal cardiac function. The authors think that carbon dioxide is the most useful means for inducing local cardiac hypothermia, as it has not only the physical effect of lowering the local temperature of the heart but also a chemical antifibrillating and bradycardic effect.

Consideration of 94 Cases of Embolism of Peripheral Arteries. R. Fontaine, M. Kim and R. Kieny. Lyon Chir. 51:655-678 (Nov.-Dec.) 1956 (In French) [Paris].

Data are presented on the age distribution, causation, and location of 94 peripheral arterial emboli occurring in 72 patients. The largest age group was that from 60 to 70 years; the most frequent cause was valvular heart disease; the most frequent location was the femoral artery. Embolectomy was carried out in 29 of 38 patients seen less than 10 hours after onset of symptoms and in 23 of the 56 seen later in their plight. It was difficult to compare the 2 groups, but the only 3 deaths occurred in the group in which operation was delayed. There were also 11 amputations in this group as compared with 2 in the group seen early. The authors conclude that arterial embolism is an emergency that should be referred immediately to the surgeon, who will decide between embolectomy and conservative medical management. Five cases are described in detail. In one instance a large embolus was removed from the bifurcation of the aorta with complete relief of symptoms; a photograph of the embolus is given with oscillographic and other data showing the restoration of normal blood flow in the extremity. In another case the removal of a clot 75 cm. in length from the femoral artery was followed by complete recovery. Two arteriograms show the fineness of detail attainable by the use of roentgenography, essential for exact diagnosis. The authors believe that physicians should be alerted to the need for prompt action in peripheral arterial embolism; that the best treatment is embolectomy if it can be done before the 10th hour; and that this operation is scarcely worth the effort after that time. In patients seen later, the preferred operations are lumbar sympathectomy, or arteriectomy with or without a vascular graft, or the arteriovenous shunt. Medical treatment is reserved, in the opinion of the authors, for patients with mild cases or in bad general condition.

Myxoma Cordis: Diagnosis Established Pre-operatively: Surgical Removal of the Tumour. F. S. P. Van Buchem and L. D. Eerland. Dis. Chest 31:61-73 (Jan.) 1957 [Chicago].

Myxoma cordis is rare, 128 cases having been reported up to 1951. There has been some controversy as to whether these formations are organized thrombi or tumors. They are now regarded as tumors, in fact the most frequently occurring primary tumors of the heart, accounting for about 50% of all primary cardiac tumors. About half of the cardiac myxomas are polypous neoplasms of a partly gelatinous, partly rubbery consistency, as a rule with a pedicle, arising from the auricular septum close to the foramen ovale. Three-fourths of these tumors are situated in the left atrium. They have been observed in all age groups in both sexes, but mainly between the 30th and 60th year of life. The size may vary from that of a pea to that of a closed fist. The small tumors cause no symptoms. The authors report the clinical history of a 45-year-old man in whom the diagnosis of pediculated myxoma cordis originating from the septum of the left atrium was established before the operation.

It was decided to operate with the patient under hypothermia, although there was little promise of success in view of the patient's age and serious pulmonary hypertension and the attack of decompensation. Cardiac fibrillation was an imminent danger. The immersion cooling technique was employed. After the temperature had fallen 1 C cardiac arrest occurred, most probably due to obstruction of the mitral ostium by the lower pole of the tumor. Cardiac rhythm was restored by means of heart massage, and the operation was terminated transatrially without any loss of blood or air embolism. Unfortunately, ventricular fibrillation started shortly afterwards; although this was overcome in the beginning, death was unavoidable due to repeated ventricular fibrillation. The tumor measured 6.5 by 4 by 5 cm.

Recurrent Lipoma of Floor of Mouth. P. de Castro Correia. Rev. Paulista med. 49:281-286 (Oct.) 1956 (In Portuguese) [Sao Paulo, Brazil].

A 25-year-old woman requested removal of a huge tumor of the mouth and the mandible. Her parents said that she had been normal up to the age of 4 years, when a tumor started growing on the floor of her mouth. When she was 8 years old, the tumor had reached the size of a hen's egg. The tumor, which included a segment of her mandible, was removed. It started growing again 1 year after the operation and became huge in 6 years. The range of the patient's voice changed, but she had no difficulty in taking food or liquids. The tumor involved all of her chin and a segment of the left submandibular region. It was removed in 2 stages in 1945 (when the patient was 14 years of age) and again in 1946, 1952, and 1953. The histological examination of the removed specimens showed lipoma until 1953, when it showed adipose sarcoma. During the last operation, it was observed that the tumor involved the lower aspect of the tongue and the floor of the mouth. Previous operations had failed to remove all of it. Follow-up observation in 1954 did not show any recurrence. The mandible was then reconstructed with a bone graft. The results were satisfactory, but in 1956 the tumor was found to be growing slowly.

NEUROLOGY & PSYCHIATRY

Carotid Sinus Epilepsy and Its Treatment by Denervation. S. Behrman and G. Knight. Brit. M. J. 2:1522-1524 (Dec. 29) 1956 [London].

The authors report a case of carotid sinus epilepsy in a 47-year-old man who had "blackouts" that were preceded by a momentary "whirlpool" sensation. Attacks were occasionally provoked by rotating the chin to the left with the head in the position of extension, as when the patient was reclining in an easy chair. The period of unconsciousness was usually of a few minutes' duration, and there were no convulsive movements. The patient remained flaccid during the attacks, without any detectable change in pulse or breathing. He complained of intense headache immediately on regaining consciousness and as a rule passed into a deep sleep. Compression in the region of the right carotid bifurcation provoked within 15 to 30 seconds the familiar "whirlpool" sensation usually preceding his attacks of unconsciousness. There was no associated change in pulse rate or blood pressure. The electroencephalogram showed generalized paroxysmal theta dysrythmia on hyperventilation. Denervation of the right carotid sinus was performed in November, 1954, and since then the patient has remained free from blackouts and it is no longer possible to induce vertigo by pressure in the region of the right carotid sinus. A few similar cases were collected from the literature.

A state of unconsciousness can be induced rapidly in a few persons by stimulation of an overactive carotid sinus. There is no demonstrable change in cerebral blood flow during the period of unconsciousness, and a transient delta rhythm may make its appearance. This response is no longer obtainable after carotid sinus denervation. The evidence points to an epileptic causation of unconsciousness. The syndrome should be classed with sensorily precipitated epilepsy. Carotid sinus epilepsy is one example of a wider pathological phenomenon whereby the stimulation of certain receptors that ordinarily give rise to cardioinhibitory reaction may instead produce epileptic activity.

Use of a Chlorpromazine-Dextro-Amphetamine Combination in Anxiety Neuroses. T. M. Hart. Am. Pract. & Digest Treat. 7:1988-1990 (Dec.) 1956 [Philadelphia].

Chlorpromazine and dextro amphetamine sulfate, a depressant and a stimulant of the central nervous system, respectively, have generally been administered separately. Since "associated" or secondary depression and fatigue often complicate neurotic disturbances, a combination of the two drugs seemed to promise advantages over the use of chlorpromazine alone. A combination of these two agents is now available in 5:1 chlorpromazine–dextro amphetamine ratio in 2 strengths: 25 mg.-5 mg. and 10-mg.-2 mg. Both drugs have been used in neurotic states and in acute and chronic alcoholism. The selective central nervous system action of chlorpromazine provides detached calm without suppression of mental faculties. The stimulation of dextro amphetamine increases psychomotor activity, counteracts depression, and lessens the sense of fatigue. The combination of chlorpromazine and dextro amphetamine was administered in office practice to 24 patients, chiefly anxious neurotics and alcoholics. After some initial treatment with the 10 mg.-2 mg. tablets, all patients received 25 mg.-5 mg. tablets either 3 or 4 times a day.

Results were excellent in 14 patients, good in 6, and poor in 4. The few side-effects consisted of moderate genitourinary complaints in 1 patient, moderate anorexia in 1, moderate drowsiness in 1, and overstimulation, presumably by dextro amphetamine, in 2. The combination provided relief from anxiety and apprehension in neurotics and controlled psychomotor agitations, emesis, and delirium tremens in alcoholics. Patients in both groups showed increased energy and renewed interest in their activities.

Long-Term Effects of Phensuximide (Milontin). J. Rey-Bellet and W. G. Lennox. A. M. A. Arch. Neurol. & Psychiat. 77:23-27 (Jan.) 1957 [Chicago].

The authors report a 2-year follow-up study of 249 children with epilepsy after they had been given phensuximide (Milontin) for 1 to 3 years. One hundred fifty-eight of the 249 patients had petit mal epilepsy, 114 had grand mal, and 117 had focal seizures. Many patients had more than 1 of the 3 forms of seizures. The number of patients with 90% to 100% control of attacks was greater at the end of the 2-year period than at its beginning in each of the 4 categories. The gain was small, from 2 to 5 percentage points.

There was, however, a decrease in the number of patients with from 50% to 90% improvement. With respect to over-all benefit, the number of patients with an improvement greater than 50% fell from 31% to 27% in the course of 2 years. These follow-up results were less satisfactory than those reported by Zimmerman, who pioneered in the use of phensuximide but perhaps used more previously untreated patients than the authors did.

As a rule, early improvement correlated with continued improvement. Seventy-six per cent of patients with initial excellent control of petit mal maintained that position 2 years later, and 25% of these had discontinued treatment with phensuximide. Seventy-five per cent of those with grand mal or focal seizures maintained the position of initial excellent control, but only 3% had discontinued treatment with phensuximide. Among those with initially good control, 35% of patients with grand mal or focal seizures and 24% of patients with petit mal had achieved excellent control by the time of the authors' study. Thus, benefit from treatment was prompter and more lasting for patients with petit mal, but convulsive attacks tended to improve with time. If initial improvement was less than 50%, very little was gained by a longer trial.

The authors believe that trimethadione (Tridione) is more likely to produce dramatic control of pure petit mal than phensuximide. Trimethadione carries a small risk of bringing on convulsive attacks or harmful side-effects. Phensuximide seems to be without serious side-effects and has a beneficial effect on grand mal and focal seizures as well as on petit mal. There is some loss of effectiveness for some patients with passage of time, but probably the loss is no greater than that for other anticonvulsants.

A New Congenital Non-progressive Myopathy. G. M. Shy and K. R. Magee. Brain **79**:610-621 (Dec.) 1956 [London].

Diseases of skeletal muscle occurring during the neonatal period are generally separated into 2 groups. The largest group includes infants with weakness and hypotonia (flabby infants). The smaller group are those with myotonia and no demonstrable weakness (myotonia congenita). The authors are concerned with the first group. Myotonia and muscular weakness in infancy may have many causes, such as mental retardation, rickets, cretinism, myasthenia gravis, achondroplasia, and infantile scurvy. After these disorders are eliminated, there remain 3 groups: (1) progressive spinal atrophies of infancy (Werdnig-Hoffman's disease); (2) progressive muscular dystrophy of infancy (both of these disorders supposedly are progressive); and (3) a symptom complex reported by Oppenheim in 1900 in which he described infants who were flaccid from the time of birth and whose extremities could be placed in bizarre postures.

The authors took muscle biopsy specimens from 3 infants. The microscopic findings were similar to those described by Spiller, in that small fibers were present. The final outcome in these cases is unknown. The only ways to demonstrate nonprogression are examinations on several generations in a heredofamilial disease. The authors report studies on 5 patients in 3 generations of the same family with a nonprogressive myopathy. The disease was probably congenital or developed within the first months of life. Muscular weakness was proximal and most severe in the lower extremities, but some proximal weakness in the upper extremities was suggested by history or examination in all cases. This disorder results in delayed walking. When the children do learn to walk, their disability remains stationary. Hypotonia was evident in the children reported on, but the tendon reflexes were normal, and wasting was not a prominent feature. There were no associated sensory disturbances. The cranial nerves were normal with the exception of weakness of the sternocleidomastoid muscles and the orbicularis oculi in one patient. The principal histological change was in the anatomic arrangement and histochemical characteristics of aberrant fibrillary bundles found in the center of almost every muscle fiber. Frequent large fibers and central nuclei were the other characteristics of the disease.

Serial Liver-Function and Blood Studies in Patients Receiving Chlorpromazine. R. Dickes, V. Schenker and L. Deutsch. New England J. Med. **256**:1-7 (Jan. 3) 1957 [Boston].

Fifty psychotic patients treated with chlorpromazine have been studied serially for changes in liver function and blood morphology. Twenty-one patients showed abnormalities of liver function during the course of treatment. Function returned to normal in 13 of these patients, despite continued treatment. Treatment was stopped in the remaining patients. Serial testing enables one to determine the presence of progressive abnormality severe enough to warrant stopping treatment. In this series of patients bromsulfalein retention and alkaline phosphatase were the most sensitive and the earliest indicators of liver dysfunction due to chlorpromazine. Patients with preexisting minor liver damage were no more likely to have liver impairment from chlorpromazine than those with normal liver function. Hematological abnormalities, including leukopenia, eosinophilia, and immature cell forms, were often noted. In many cases these changes occurred in patients with liver dysfunction. Developing leukopenia occurring in the course of treatment is considered a contraindication to further treatment with chlorpromazine.

Observations on Hospitalized Adolescent Drug Addicts. P. Mason. New York J. Med. **57**:67-70 (Jan. 1) 1957 [New York].

There seems to be a difference in the severity and the duration of the withdrawal sickness between the adult and the adolescent addict. There are several reasons: The general physical condition of the adolescents is better than that of the adult addicts. The period of addiction is relatively short. The adolescent addicts are in the 16-to-21-year age group, and the duration of the addiction is on the average about 2 years, with a few exceptions up to 5 years. The amount

of drug consumed is usually about 2 "bags" of heroin a day. Since a "bag" contains about 1/64 grain of heroin and since the drug is no more than 1 to 3% pure, the actual amount of drug taken is small. The rehabilitation and psychiatric treatment of the adolescent drug addict involves many obstacles. The majority come to the hospital because of outside pressures rather than their own desire for help. These outside pressures may be the choice given by the judge between jail and the hospital; the feeling that the police are closing in; the threats, pleas, or cajoling of the family. Many times the family's attitude is such as to make the patient's feeling that he is being punished quite understandable. The patient is then physically present and accessible to ministrations, but his basic lack of motivation and overt resentment against this enforced treatment make his psychological cooperation difficult.

The patient may pit against each other the different members of his family, the hospital staff, and the different agencies concerned with his welfare, creating confusion, misunderstanding, and at times ill feelings. Close liaison and frequent detailed communication among the different persons concerned with the treatment of the patient are important. From the viewpoint of "symptom choice," addiction may not only express a person's rebellious tendencies but also may have an integrative role. One of the illustrative case histories suggests that heroin helped the patient to master some conflicts that his tottering defenses could not handle otherwise. This applies to a whole gamut of conditions (schizophrenia in all of its forms and degrees; the inadequate personality syndrome) and symptoms such as hostility, obsessive thinking, anxiety, delusions, and sexual impulses. The patient may thus be able to handle certain problems by denying their existence, diminish the intensity of others, and strengthen his ability to cope with still others. However, the author does not wish to suggest the use of narcotics as a treatment of certain psychiatric disorders.

GYNECOLOGY & OBSTETRICS

Value of Cytology in Gynaecology. H. C. McLaren, C. W. Taylor and M. E. Attwood. J. Obst. & Gynaec. Brit. Emp. **63**:801-811 (Dec.) 1956 [London].

A cytology laboratory was established at the Hospital for Women in Birmingham. The technicians of the gynecologic laboratory received training in the method from Papanicolaou and others in the United States. There was no medically qualified cytologist at the Birmingham hospital, but the trained technicians were responsible for the cytological tests. Generally, 6 months was necessary for the technicians to become efficient. Material for smears was obtained by the vaginal aspiration technique in the hands of the cytologist or her trainees. This method had the advantage over Ayre's scraping of the portio vaginalis in that the vaginal smear, the taking of which does not require a speculum, contained many cells from the endometrium and endocervix as well as from the portio vaginalis. If the smear was unsatisfactory a further smear was taken. An exact assay of the value of cytology in a service not specializing in cancer detection was attempted. It was found that ocular fatigue limits microscopy to 3 or 4 hours, or about 16 to 18 slides a day. A vaginal smear cannot be read accurately in less than 7 minutes per slide; 10 minutes is nearer to the average. In the first 2,250 patients examined by the clinicians, the following diagnoses were attributable to the cytological studies: 1 carcinoma of the corpus uteri, 1 invasive carcinoma of the cervix, and 8 carcinomas in situ. Errors in cytological interpretation were the following: 11 false-positive smears (17% of all positive smears or 0.5% of all smears) and 6 false-negative smears (10% of the malignant lesions or 0.26% of all smears).

Results of Delivery by Cesarean Section in the Years Between 1928 and 1951. J. Weilenmann. Gynaecologia **142**:403-413 (Dec.) 1956 (In German) [Basel, Switzerland].

In a series of 23,112 deliveries, 590 (2.55%) were carried out by cesarean section. The abdomen was opened by median laparotomy. The uterine cavity was opened by a deep longitudinal incision in the period between 1928 and 1936, but the transperitoneal cervical transverse section has been gaining in popularity since 1936. Ether or a mixture of chloroform and ether was used for the relief of pain, mostly after the intravenous administration of a basic narcotic, in the earlier years. Thiopental sodium was used in later years, and at present the sodium salt of 1-methyl-5,5-allylisopropyl barbituric acid (Narconumal) is used because it passes more slowly into the fetal blood. Only 1 of the 327 women in whom this type of anesthesia was used died during the anesthesia. One hundred thirty-one women were operated on with the aid of spinal anesthesia with α-butyloxycinchoninic acid–diethylethylenediamide (Percain) hydrochloride; one of these patients died of cessation of breathing. One hundred twenty-seven women were delivered with the aid of local anesthesia and nitrous oxide, 3 with the aid of caudal anesthesia, and 2 with perdural anesthesia. Cesarean section was performed in the interest of the mother in 356 deliveries, in the interest of the infant in 91, and because of widened indications (primipara of advanced age, pregnancy continued beyond term, abnormal labor pain, and abnormal presentation) in 143. Contracted pelvis and disproportion between the head and the pelvic outlet was the most frequent indication and occurred in 139 (23%) of the 590 deliveries. Repeated cesarean section was performed in 104 women; 100 had 2 and 4 had 3 cesarean sections. Three of the 104 women died, and death was attributed to the operation in 1.

In the entire series 18 (3.05%) of the mothers died, 8 from eclampsia, 5 from peritonitis, 1 from pulmonary embolism, 1 from cardiac decompensation, 1 from hemorrhage, and 1 from anesthesia; in 1 no cause was stated. The corrected mortality rate was, therefore, 1.69%. Eight of the 10 patients who did not have eclampsia died before the advent of antibiotics. Six hundred three infants (13 twins) were delivered by

cesarean section and 50 of them died, a death rate of 8.29%. Death was attributed to the operation in 41, a corrected mortality rate of 6.8%. Disturbances of the puerperium occurred in 183 women (31.9%).

PEDIATRICS

Observations on the Clinical Use of V-Cillin in Pediatric Practice. M. Alvarez-Pagan, D. C. Rees and G. F. Conway. J. Pediat. **50**:39-43 (Jan.) 1957 [St. Louis].

The acid stability of phenoxymethyl penicillin (penicillin V) has been established. V-cillin is a fruit-flavored pediatric oral suspension of penicillin V. This form of penicillin V was used to treat respiratory tract infections in 84 children observed in a general pediatric clinic practice. It was well accepted and tolerated without notable side effects by 78 of the 84 patients. Penicillin V proved to be clinically effective in combating the respiratory tract infections due to hemolytic streptococci, Staphylococcus (Micrococcus) aureus, and Diplococcus pneumoniae. Results compared favorably with those that might have been expected from the intramuscular administration of 300,000 units of procaine penicillin G twice daily. Consequently the authors feel that in children the majority of respiratory infections requiring penicillin therapy may be treated successfully with oral penicillin V. Since the blood level of penicillin V begins to decline after 4 hours, with detectable levels remaining 6 hours after oral administration, the authors gave 250 mg. (400,000 units) as the initial dose and 125 mg. (200,000 units) every 4 hours or 4 times a day.

Vaccination with Avianized Smallpox Vaccine. M. Weichsel and E. G. Herrera. J. Pediat. **50**:1-5 (Jan.) 1957 [St. Louis].

This report is concerned with observations on children vaccinated with chick embryo–type vaccines. Glycerinated chick embryo vaccine was administered to 285 children; sorbital-stabilized fluid chick embryo vaccine to 44 children; and vacuum-dried, sorbitol-stabilized chick embryo vaccine to 85 children. The children ranged in age from 3 months to 12 years. The results were satisfactory, with a large percentage of susceptible children showing primary takes. Side-reactions were mild, and no complications ensued. The advantages of employing vaccinia virus material prepared on the chorioallantoic membrane of the developing chick embryo are discussed.

The Use of Dermal Configurations in the Diagnosis of Mongolism. N. F. Walker. J. Pediat. **50**:19-26 (Jan.) 1957 [St. Louis].

Clinical evidence alone is frequently not sufficient to establish whether a child is a mongoloid imbecile, particularly in the case of a newborn infant. The author outlines an objective method, which is based on the significant differences in the frequencies of dermal configurations for mongoloid imbeciles compared with a control series. It was found that 70% of mongoloid imbeciles possess combinations of patterns not repeated in nonmongols, while 76% of the nonmongols have combinations not found among the imbeciles. The dermal configurations used are the finger patterns and certain of the palm and sole patterns. There still remains the problem of the overlap between the mongols and controls, and in future calculations the author plans to use additional characters such as the presence of a single crease on the fifth digit, the single simian crease on the palm, and the speckling of the iris. With the addition of these and other characters it is hoped that the overlap will be reduced. The association of patterns is also being investigated.

UROLOGY

Further Experience in the Treatment of Vesical Tumors with Interstitial Radioactive Cobalt. V. Vermooten. J. Internat. Coll. Surgeons **27**:31-35 (Jan.) 1957 [Chicago].

Twenty-two patients with infiltrating carcinoma of the bladder were treated with radioactive cobalt (Co^{60}) in nylon sutures used as an implant at the periphery of the growth to destroy the invasive cells. Five of the patients died, 1 of myocardial failure, 1 of pneumonia, and 3 of metastases to the liver and elsewhere. One patient, although he has lived 1 year since the operation, still has carcinoma. Sixteen patients are well and have been free from the disease for periods varying from 3 months to 4 years.

These results convinced the author that carcinoma of the bladder should be divided into 3 main categories for the purpose of treatment. First, there are the benign papillomas, which are noninvasive, single or multiple, and often recurring growths that may be considered a disease of the entire vesical mucosa. This disease is automatically eliminated as a tumor that should be treated with interstitial irradiation unless and until some tumors of this type become actively infiltrating and invasive. At that time they change their classification into the 2nd group, which consists of the solitary, actively invasive, infiltrating carcinomas. It includes the sessile tumor, the flat-growing infiltrating tumor, and the superficially ulcerating squamous cell type of growth. Any tumor of the bladder that invades the tunica propria or muscularis is included in this group. Interstitial Co^{60} is the method of choice for the treatment of all these tumors. The 3rd group is composed of tumors that have grown through the wall of the bladder and invaded the perivesical tissues. Most of the tumors of this type have been previously operated on by extensive segmental resection including a large cuff of normal adjacent bladder wall. Recurrence after such an operation means that the carcinoma is outside as well as inside the bladder and that one can do little, even in the way of palliation, for such a patient.

All of the 16 patients who were treated with interstitial Co^{60} and whose lesions were confined to the vesical wall now have normal bladders and void normally. Co^{60} in nylon sutures used as an implant represents a source of radiation that can and does furnish a carcinocidal dose to a localized area more readily and more accurately than it can be delivered by any other method. Thus, by using interstitial radiation one can achieve the same result as by total cystectomy, with the great advantage that the patient is left with a normal urinary tract instead of a cloaca or the necessity of wearing some "device."

The Reliability of the Papanicolaou Technique when Cancer Cells Are Found in the Urine. S. I. Roland and V. F. Marshall. Surg. Gynec. & Obst. 104:41-44 (Jan.) 1957 [Chicago].

Cytological studies of the urine by the Papanicolaou method were made on patients of the New York Hospital–Cornell Medical Center, where 6,740 specimens of urinary sediment from 2,414 patients were investigated, an average of 2.79 specimens per patient. The presence of malignant neoplastic cells (classes 4 or 5) was indicated in 442 (6.5% of the 6,740 specimens). These 442 specimens were obtained from 176 patients, that is, cancer cells were found in the urinary specimens of 176 (7.2%) of the patients. Follow-up data for 5 years are available in all but 1 of the 176 patients. Because the objective was to determine the reliability of the reports indicating the presence of cancer, not to evaluate the sensitivity of the test, there was no follow-up in the other cases. Cancer has not been demonstrated in 8 (4.6%) of the 176 patients. Five of the 8 patients have been followed for 5 or more years, 2 have died without evidence of cancer prior to the lapse of 5 years, and 1 patient has disappeared from follow-up examination after 8 months. The 4.6% of false-positive tests is small enough to justify suspicion of the existence of a urinary cancer whenever the Papanicolaou tests reveals cancer cells in the urinary sediment. An unexplained positive report warrants following the patient for an indefinite period of time. The Papanicolaou method provided early evidence of cancer in a number of cases even before careful urologic examination. Some of these cases are briefly described. Studies of exfoliated cells in the urine proved especially valuable in cancers arising from the transitional epithelium. Cancers of the renal parenchyma and small prostatic cancers were not often detected by this method; but when cancer cells were found in such cases, the positive report was reliable. Cytological studies did occasionally push back the point of recognition of such disease and make possible its early diagnosis.

The Use of the Intestine in Urology: Omitting Ureterocolic Anastomosis. C. A. Wells. Brit. J. Urol. 28:335-350 (Dec.) 1956 [Edinburgh].

Wells reports on 323 patients with diseases of the genitourinary tract who were treated surgically. Of these, 212 had an ileal ureterostomy, 56 had ileal replacement of the ureter and ureteroileocystoplasty, and 55 had an ileocystoplasty. Fifty-six of the 212 patients died in the hospital, a mortality rate of about 25%. Ninety-two of the 212 had ileal ureterostomy combined with cystectomy for carcinoma of the bladder, and 29 of these died; only 4 of 45 patients with congenital deformity associated with incontinence died. Complications of the operation occurred in 120 patients; ileus with or without obstruction was the main cause of death. Ileal ureterostomy alone in good-risk patients with nonmalignant disease is not a particularly dangerous procedure. Pyelitis was recorded in only 11 of the 156 patients who survived the operation. The absence of evidence of pyelitis as a late phenomenon in ileal ureterostomy was the most striking feature. The blood chemistry was virtually unchanged by ileal ureterostomy. Physical development, appetite, weight, healthy general appearance, and normal vigor were constant features in the surviving patients. The need to wear a bag was accepted by most patients as the price of good health. Thirty-three of the 156 discharged patients died after leaving the hospital. Of the 33 deaths, 24 occurred in 65 patients with carcinoma of the bladder who had undergone cystectomy combined with ileal ureterostomy and 9 occurred in 91 patients with other diseases of the genitourinary tract. The contrast between the patients with malignant and nonmalignant disease and the highly satisfactory survival rate in the nonmalignant group emphasize the fact that renal complications do not preponderate as a cause of death.

Of the 56 patients with ileal replacement of the ureter and ureteroileocystoplasty, 4 died in the hospital. Twenty-eight were followed up for an average period of 12 months. Results were excellent in 6, good in 13, satisfactory in 5, and fair in 1; there were 3 therapeutic failures. Renal function was preserved or improved and symptomatic relief was obtained in patients with increased frequency and urgency. Clinical assessment was available several months after the operation in 39 of the 55 patients with ileocystoplasty. Excellent results were obtained in 21 who were relieved of all symptoms. The degree of relief of pain and frequency justified the operation in 6 of every 7 patients. Of the 50 patients leaving the hospital after ileocystoplasty, 1 died within the first 6 months and 1 after 18 months; the remaining 48 survived.

Investigations on the Secretory Function of the Kidney After Splanchnicotomy. H. Dettmar. Ztschr. Urol. 49:633-640 (No. 11) 1956 (In German) [Leipzig, Germany].

It has been suggested that in patients with renal calculi the removal of the concretion should be combined with the denervation of the kidney. It is hoped that this will increase the blood circulation through the organ and that then a less concentrated urine will course more freely through the renal channels and the recurrence of calculi might be prevented. The authors mention a number of investigators who either after

total denervation of the kidney or after splanchnicotomy were able to demonstrate increased blood circulation as well as the excretion of larger quantities of a much less concentrated urine. Although it remains conjectural to what extent the observations in experiments in animals can be applied to human subjects, it is pointed out that Verney in experiments on dogs observed no change in the diuresis after splanchnicotomy. Because of these contradictory results of renal denervation in experiments in animals, the author investigated the urinary excretion after splanchnicotomy in human subjects. Ten patients (6 women and 4 men) had been hospitalized on account of severe recurring renal colic. Clinical and roentgenologic studies revealed no mechanical cause for these colics, but in all 10 patients the renal pelvis was of ampullary shape, and tests showed a reduced urinary evacuation. A diagnosis of severe recurrent renal colics due to painful hydronephrosis was made.

In the course of the operation, after the greater splanchnic nerve had been identified a loop was placed around it and it was divided where it emerges from the diaphragm; then it was grasped with a long clamp and was resected with the lateral portion of the semilunar ganglion and with the caudally located aorticorenal ganglion. Then the lesser splanchnic nerve was sought somewhat deeper down. Several fibers may be found, which under spatular pressure on the peritoneal sac may be seen to pass in a medial direction. These fibers should be divided. After that the ureter should be inspected at the point of its emergence from the renal pelvis to exclude a mechanical obstruction.

After the operation the renal function of the patients was tested with the aid of water and concentration tests. It was found that the denervation of kidneys with normal secretory function does not produce changes in the renal ability to concentrate urine nor in the quantity of urine. Observations on these 10 patients led to the same results that Verney obtained in dogs but disproved the observations of other investigators. If splanchnicotomy retards or prevents the formation of urinary calculi, it does not accomplish this effect by increased renal perfusion with a urine of low concentration, but other factors must play a part.

THERAPEUTICS

Clinical Observations on the Use of a Combination of Reserpine, Quinidine, and Adenosine Given to Patients with Cardiac Arrhythmias or Coronary Heart Disease. A. Agnoletto. Minerva cardioangiol. 4:622-630 (Oct.) 1956 (In Italian) [Turin, Italy].

Tablets containing a combination of reserpine (0.1 mg.), quinidine (100 mg.), and adenosine (2 mg.) were used for the treatment of 22 patients with cardiac arrhythmias or coronary heart disease. Six patients had extrasystoles, in 4 due to organic disturbances and in 2 due to functional disturbances; 6 had tachycardia, in 4 due to myocardiopathy and in 2 due to distonia or hyperthyroidism; 5 had auricular fibrillation; and 5 had angina pectoris, caused by organic disturbances in 3 and by functional disturbances in 2. The beginning dose was 3 to 5 tablets per day and the maintenance dose was 1 to 3 tablets per day. The objective and subjective results obtained were good. The best results were obtained in patients with tachycardia and in patients with extrasystoles. Patients with auricular fibrillation were first treated with digitalis and quinidine and then with the combination in stabilizing dose. Cardiac insufficiency, when present, regressed relative to the amounts of the combination that the patient received. Electrocardiograms did not change markedly. Normal or low blood pressure values do not contraindicate treatment with this combination.

Polyneuropathy as a Complication of Disulfiram Therapy of Alcoholism. M. Hayman and P. A. Wilkins. Quart J. Stud. Alcohol 17:601-607 (Dec.) 1956 [New Haven, Conn.]

The authors report on 4 men and 3 women between the ages of 21 and 55 years in whom some form of polyneuropathy developed in the course of treatment of alcoholism with disulfiram (Antabuse). They were given 2 gm., 1.5 gm., 1 gm., and thereafter 0.25 to 0.75 of the drug on successive days. Disulfiram-alcohol reactions, with the equivalent of 8 to 15 cc. of absolute alcohol, were evoked usually on the 5th and 8th days, then once a week for several weeks, then once a month, and finally every 2 months to the end of the year. There were usually 12 disulfiram-alcohol tests during the course of the 1st year of treatment. There was no previous history of polyneuropathy in these patients, and the alcoholism was well controlled. Motor and sensory changes, including incoordination, hypesthesia, decreased or absent knee and ankle jerks, numbness and tingling of the extremities, and a steppage gait, developed gradually over a period of 4, 5, 7, 8, 9 and 12 months, respectively, in 6 of the 7 patients. Upper and lower extremities were involved in 3 patients and the lower extremities alone in the 3 others. The polyneuropathies in these 6 patients were probably caused by chronic intoxication with disulfiram. An elevation of the total protein level was found in both patients whose spinal fluid was examined. The 7th patient, a 55-year-old man who had been drinking excessively for 25 years, had absent knee and ankle jerks, numbness and tingling of the lower extremities, a steppage gait, and involvement of both upper extremities on the day after his first disulfiram-alcohol test. The reaction to this test was a severe asthma-like attack and mild delirium lasting for 3 hours. The specific, precipitating disulfiram-alcohol test, the rapid onset and recovery, the concurrent asthma-like symptoms, and the remission after the use of antihistamines suggested an allergic reaction to the test. The symptoms invariably disappeared in all patients after a few months. In essence, the treatment consisted of administration of polyvitamins and withdrawal of disulfiram.

The patients often required larger doses of disulfiram for adequate protection than is generally reported. One patient could drink with a maintenance dose of over 1.5 gm. and required 2 gm. daily for any degree of protection. Patients who require the larger doses should be kept under close observation for premonitory symptoms of polyneuropathy. Each patient treated with disulfiram should be routinely questioned and examined for evidence of polyneuropathy. Should the disease be present in mild form, lower dosage may be sufficient to guard against its progression. Should the disease be more severe or should it advance if the dose is lowered, the drug should be withdrawn. The diagnosis may be established by examination of the spinal fluid and demonstration of albuminocytological dissociation.

On the Possible Therapeutic Uses of Trypsin: Effect of Intramuscular Injections of Trypsin in Patients with Thrombophlebitis or Phlebothrombosis. S. Serrano. Minerva cardioangiol. 4:630-633 (Oct.) 1956 (In Italian) [Turin, Italy].

Pure trypsin in a sesame oil suspension was injected intramuscularly in 16 patients with thrombophlebitis or with phlebothrombosis. The results obtained were satisfactory. Edema and pain tended to disappear. The preparation has a marked anti-inflammatory effect relative to the dose that the patient receives. The author experimented first with a dose of 1 cc. (5 mg.) every 8 hours and then with a dose of 0.5 cc. (2.5 mg.) every 6 hours. The optimal dose was established as 1 cc. and 0.5 cc. alternately every 6 hours. Patients with mild forms of the disease received a reduced dose. The preparation was well tolerated even when the treatment was continued for 10 to 15 days. Anticoagulants were combined with the trypsin therapy. Clinical data showed that the enzyme improves the effect of anticoagulants.

Attempt at Treatment with Para-(Di-2-Chloroethylamino)-Phenylbutyric Acid of Hodgkin's Disease, Chronic Lymphoid Leukosis, and Various Sarcomas of the Lymphoid Tissue: A Study on 100 Patients. J. Bernard, G. Mathé and M. Weil. Rev. franç. études clin. et biol. 1:1121-1132 (Dec.) (In French) [Paris].

The authors report on 100 patients, among them 12 children, with Hodgkin's disease, chronic lymphatic leukemia, or lymphosarcoma and reticulosarcoma. Para-(di-2-chloroethylamino)-phenylbutyric acid was given by mouth and generally had few side-effects. No toxic effects occurred with small doses of the drug (0.1 mg. per kilogram of body weight per day). Pancytopenia with medullary hypoplasia or aplasia was observed in Hodgkin's disease by giving larger doses of the drug. Cortisone or prednisone reduced the incidence and severity of the complication. Remarkably good results were obtained in 40 patients with chronic lymphatic leukemia. The hemogram of 23 of these patients was brought to normal and all clinical symptoms disappeared during treatment with the drug. Fourteen patients showed moderate improvement, and in only 3 could no benefit be observed. Good results were less frequent in Hodgkin's disease. Seventeen patients of 52 had a definite and prolonged recovery, 15 had moderate improvement, and no benefit was seen in 20. Pruritus and skin manifestations were relieved, but fever and glandular enlargement did not disappear so frequently, and pain did not subside. Prolonged remarkable recovery was obtained by treatment with the drug in 7 patients with lymphosarcoma or reticulosarcoma. Three patients showed moderate improvement and 3 had no benefit. Para-(di-2-chloroethylamino)-phenylbutyric acid is easy to handle and produces few undesirable side-effects. It offers the best kind of treatment for chronic lymphatic leukemia, particularly when given in small doses. Better results are obtained when the drug is given in addition to cortisone.

Advanced Cancer Treatment with Nitromin. B. A. Stoll. M. J. Australia 2:882-887 (Dec. 15) 1956 [Sydney].

Nitromin, a nitrogen mustard, is chemically described as methyl bis (β-chlorethyl) amino-N-oxide hydrochloride. The drug has been used in 15 patients with advanced cancer and in 4 with malignant lymphoma. Nitromin has no vesicant action on the skin or mucosa if it is well diluted. Its action on the blood is somewhat slower than that of nitrogen mustard, and recovery is more rapid. Leukopenia has to be watched for, as the leukocyte count usually falls. Treatment is discontinued temporarily if the leukocyte count falls to 2,000 per cubic millimeter. The hemoglobin level drops 5% to 10% after the usual course of 3 weeks' administration of the drug, but gross anemia and thrombocytopenia occur only if the administration is continued for over 6 to 8 weeks. Although nausea and vomiting often occur with the first dose, these symptoms usually disappear later. Sleepiness and dryness of the mouth are seen less often. In the rare cases in which nausea is severe after a daily dose of 50 mg., the compound can be given in 2 divided doses.

Whether Nitromin is given intravenously or orally, the dose is 1 mg. per kilogram. For adults, 50 mg. is usually given daily, dissolved in 50 cc. of isotonic sodium chloride solution and either injected intravenously or taken orally at least 3 hours after a meal or just before retiring. A full course generally comprises 750 mg. in 15 to 20 days, and response will often be apparent after the first week of administration. In the dilution mentioned the compound can also be injected intraperitoneally or directly into a tumor mass. The results were dramatic in several patients with advanced tumors, including fibrosarcoma and melanoma. In two patients in whom the tumors responded to Nitromin there had been a previous failure to respond to thio-TEPA (Triethylenethiophosphoramide) administration. Prednisolone and menadiol sodium diphosphate were given concurrently to some patients in the hope of their acting as radiosensitizers to the radiomimetic action of Nitromin.

BOOK REVIEWS

Chemosurgery in Cancer, Gangrene and Infections: Featuring a New Method for the Microscopically Controlled Excision of Cancer. By Frederic E. Mohs, B.Sc., M.D., Associate Professor of Chemosurgery, Department of Surgery, University of Wisconsin Medical School, Madison. Cloth. $13.50. Pp. 305, with 225 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1956.

To those interested in the treatment of neoplastic diseases, the work of the author in the chemosurgery of cancer over a period of many years is well known. In this handsome and profusely illustrated book the author describes the methods by which he has brought the ancient art of the treatment of surface neoplasms by means of caustic preparations to a scientific precision. In his hands, and probably in the experience of some of his pupils, the chemosurgical technique is an effective means of treatment for certain lesions, but it is a highly specialized procedure not only requiring elaborate physical resources but also imposing on the therapist the necessity of being his own microscopist. The painstaking and elaborate fixation of tissue in successive planes and the repeated removal of tissue after fixation in situ for careful microscopic examination makes the technique unnecessarily time-consuming to the professional personnel involved and much more tedious and uncomfortable for the patient than the more conventional techniques of radiotherapy and surgical excision.

Except for certain anatomic sites where maximum preservation of tissue is essential, or in certain recurrent malignant neoplasms adjacent to cartilage or to bone or possibly to important nerve trunks, the method holds no advantage over operation, irradiation, or even cautery. In chemosurgery of basal-cell carcinoma of the eyelids, where, with a distribution of lesions that in size were typical of those in most series of such patients, the author's five-year cure rate was 93.4%. Although this is a high rate of cures, MacDonald of Los Angeles has reported a cure rate of 98% in a somewhat larger series of patients with carcinoma of the eyelids than the series reported by the author. MacDonald used low-voltage x-ray therapy almost exclusively in his series. The same method of calculating end-results was employed in both instances, and fewer patients were excluded from the latter series as "dead from other causes without recurrence." The five-year survival rate of 91.7% for treatment of squamous carcinoma of the lip as quoted by the author is excellent, but there was a preponderance of cases in which the early discovery of lesions would tend toward favorable results.

In the treatment of parotid tumors by chemosurgery, the illustrations indicate a much more cicatricial and unsightly effect than would be obtained with standard surgical procedures. There is a description of some instances of lateral facial carcinoma primarily in the skin with a predilection for metastasis to cervical lymph nodes that are best treated with a combination of dissection of the neck and removal of the primary lesion. The author's statement that "dermatologists have the advantage of being able to differentiate clinically between cancer and a variety of other conditions which resemble cancer" may be true in Wisconsin but does not seem to hold true elsewhere in the United States.

Blood Group Substances: Their Chemistry and Immunochemistry. By Elvin A. Kabat. Cloth. $8. Pp. 330, with illustrations. Academic Press, Inc., 125 E. 23rd St., New York 10, 1956.

The chemistry of the blood group substances has become a matter of great concern, especially in relation to immunologic mechanisms. Immunochemistry is a highly technical field and an exacting one, but few laboratories are engaged in this work. Kabat's is one of them. His investigations have drawn heavily on the related fields of chemistry, immunology, carbohydrate and protein chemistry, genetics, and clinical medicine. The present volume synthesizes existing information on the blood substances as seen from the viewpoint of quantitative immunochemistry, and in addition presents a comprehensive review of the genetic, serologic, clinical, and anthropological aspects of the blood groups, together with a highly astute analysis of the implications of these findings. The author is well qualified for this task, especially since recent developments in his laboratory have shed the first real light on the relationship of the unique immunological specificity of the blood group A, B, and O substances to their chemical structure. Kabat's microchemical methods have been shown to be of great value in improving and standardizing preparations of blood group substances used in clinical medicine and will undoubtedly be useful in the future evaluation and reinterpretation of some of the genetics of the blood groups and in blood group serology. Several parts of the book deal primarily with clinical and serologic features of the human blood group factors. The lucid and comprehensive manner in which these topics are presented makes it possible for a person to get a broad picture of the current knowledge in this area without the prohibitive expenditure of time and energy previously necessary. Additional chapters on sources, purification, chemical composition, immunochemical characterization, and structural composition of the blood group A, B, O and Le^a substances give a detailed analysis of past work, as well as of the latest findings in the author's laboratory.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

Chapters on immunochemical similarities and dissimilarities between blood group substances and antibodies to them are also included. The bibliography is excellent. The book is highly recommended.

Synopsis of Gynecology Based on the Textbook Diseases of Women. By Robert James Crossen, M.D., F.A.C.S., Associate Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, St. Louis. Fourth edition. Cloth. $5.25. Pp. 255, with 132 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

"Diseases of Women," by H. S. Crossen, has enjoyed a period of confidence as a standard gynecologic work for over a generation. This latest edition is a compact, well-organized, and comprehensive presentation of approved principles and knowledge in this field. In every way it is worthy of its author. It includes discussions of current topics, such as the newer concepts of hormonal activity, the use of antibiotics, and psychosomatic aspects of obstetrics and gynecology. The single exception noted is the author's approval and advocacy of the use of intrauterine douches as valid treatment for postabortal infections that have already progressed beyond the confines of the endometrium and present the findings of well-developed parametritis. It would be difficult to find substantial support for this procedure among many prominent gynecologic clinicians today. In the preface to the first edition, the author rightly states: "The Synopsis will be found useful by those who desire to supplement the large book with a pocket outline for study at odd moments and memorization of the leading points in Gynecologic examination, diagnosis and treatment. No doubt the practicing physician will find it helpful as a guide to the understanding of the pelvic disturbance he may encounter or as a compact presentation of the outstanding feature of this interesting department of Medical Knowledge."

Endogenous Uveitis. By Alan C. Woods, M.D. Cloth. $12.50. Pp. 303, with 123 illustrations by Annette Smith Burgess, Instructor in Art as Applied to Medicine, Johns Hopkins University School of Medicine, Baltimore. The Williams & Wilkins Company, Mt. Royal and Guilford Aves., Baltimore 2, 1956.

This first compete textbook dealing with uveitis of endogenous origin is of great ophthalmologic importance, for it represents the accumulated information of a professional lifetime of study and research. There are chapters dealing with nomenclature, classification, and pathogenesis; the clinical findings and lesions; etiological diagnosis; and treatment. The book is well illustrated with black and white as well as numerous colored plates. The author offers plausible arguments for the classification of uveitis into the granulomatous and nongranulomatous types so long advocated by him and now widely accepted as a general classification, although many cases cannot be so sharply catalogued. His method of diagnosis and treatment of those cases of nongranulomatous uveitis believed to be of streptococcic allergic origin is described in detail and should stimulate others to similar investigations. Since many physicians fail to establish the cause of uveitis and may even fail to suspect it, this complete and up-to-date textbook should do much to encourage at least an effort on the part of ophthalmologists and internists to determine its probable cause in a higher percentage of cases. Diagnosis and treatment are fairly well established in practice, but present diagnostic methods frequently leave the question of cause in doubt. Those who seek help in solving this problem and who would appreciate a modern survey of the entire subject will do well to study this monograph.

An Atlas Illustrating the Topographical Anatomy of the Head, Neck, and Trunk. By the late Johnson Symington, M.D., F.R.C.S., F.R.S. Printed and published for Anatomical Society of Great Britain and Ireland. $21. 34 plates, boxed. Oliver & Boyd, Ltd., 39a Welbeck St., London, W.1, England; Tweeddale Ct., 14 High St., Edinburgh 1, Scotland; [Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield Ill.], 1956.

This atlas consists of detached plates of life-size horizontal sections through the head, neck, thorax, abdomen, and pelvis, with lifesize reconstructions indicating the levels of the slabs. These plates are enclosed in a portfolio designed to facilitate removal of individual figures for study or demonstration. The reprinting of this unaltered version comes 39 years after the first edition. Although the plates are clear and the labels are easy to read, the finer detail, often desired, is lacking. Although there is no accompanying text, the cross sectional anatomy presented is as representative of the normal as any single specimen, frozen and sawed, can be. No attempt has been made to indicate the range of variation that is essential to the characterization of normal topographic anatomy.

Oral Cancer and Tumors of the Jaws. By George S. Sharp, M.D., F.A.C.S., F.A.C.R., Professor of Pathology, School of Dentistry, University of Southern California, Weldon K. Bullock, M.D., M.Sc., Associate Clinical Professor of Pathology, School of Medicine, University of Southern California, Los Angeles, and John W. Hazlet, D.D.S. Cloth. $15. Pp. 561, with illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E.C.4, England. 1956.

The material in this book is based on reports of 1,020 cases collected from two institutions. Five hundred nineteen of the patients had lesions of the lip; 206, of the tongue; 128, of the alveolus; 68, of the floor of the mouth; 51, of the palate; and 48, of the cheek. The conclusions are particularly valuable since the cases presented are solely those of the authors. This work is not intended as a textbook or a reference guide but rather as a syllabus for the oral diagnosticians. The numerous photographs and roentgenograms would have been far more effective had they been in color. Chapter 4, which deals with quasi-tumors of the jaws, is especially good. Worthwhile reading references are found at the end of each chapter. Though the material should be useful to those interested in lesions, involving the oral cavities and jaws, it is refreshing to note that it is directed especially to general practitioners and dentists. This book can be recommended.

QUERIES AND MINOR NOTES

TRICHLOROETHYLENE ANESTHESIA

To the Editor:—*What is the length of time required to exhale trichloroethylene so that breathing through a soda-lime absorber will not be dangerous, as when using cyclopropane after trichloroethlyene in obstetric analgesia? I am aware that this agent reacts with soda lime to form noxious substances. Is the same true for Baralyme? This is a practical point where trichloroethylene is used as an analgesic in during labor and then a more potent agent such as cyclopropane is needed for delivery.*

Brooke F. Summerour, M.D., Dalton, Ga.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—As far as is known, no quantitative work has been done to show the time required after the use of trichloroethylene to make the use of a closed cycle with soda lime safe. This will vary with the patient and with the depth of anesthesia to which the patient has been carried with trichloroethylene. It is not considered safe practice to use the closed cycle with soda lime during any operation in which trichloroethylene has been used. Where it seems necessary to change from trichloroethylene to another agent such as ether or cyclopropane, it is common practice to continue the use of the nonrebreathing technique. In the Heidbrink Kinet-O-Meter it is a simple matter to replace the glass jar of the vaporizer containing trichloroethylene with a jar containing ether and continue on with the procedure in the same manner or to shut off the trichloroethylene and introduce cyclopropane to the gas stream. It is considered unsafe to change to the closed-cycle technique during an operation in which trichloroethylene is being used, since it is not known how long the patient will exhale trichloroethylene in sufficient concentration to cause the formation of toxic products on the soda lime. Since Baralyme is alkaline in nature, as is soda lime, and the decomposition of trichloroethylene results from the reaction with the alkaline material, it would be unsafe to use trichloroethylene with Baralyme in the closed-cycle technique.

Answer.—The introduction of cyclopropane for use in a nonrebreathing technique increases the explosion hazard. Although it may be pointed out that the introduction of ether will cause the same hazard, experimental findings reported by the Bureau of Mines show that the spark energy needed to set off an explosion with cyclopropane is very small as compared to ether. However, they have also shown that the addition of helium to the mixture increases almost 10 times the amount of spark energy necessary to set off an explosion with the use of cyclopropane.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

ANALEPTICS FOR BARBITURATE INTOXICATION

To the Editor:—*There is apparent agreement between most authors concerning the basic supportive therapy of acute barbiturate intoxication. A main point of contention, however, arises over the indications for the use of analeptics. The use of Megimide and Daptazole in the treatment of acute barbiturate intoxication as specific antagonists to barbiturates has been reported. What is the current status of the use of analeptics in acute barbiturate intoxication and are Megimide and Daptazole available in the United States for therapy or clinical trial?*

Jack H. Burnett, M.D., Emory University, Ga.

Answer.—Whether analeptics should be used in the treatment of acute poisoning with barbiturates is a matter of opinion. It is difficult to reach a decision on the basis of the clinical literature, because of the large number of factors that affect the mortality rate. Such factors include the type of barbiturate ingested, total dose taken, age, physical status, length of time since ingestion of the barbiturates, variation in exposure to cold, aspiration of vomitus, and the intensity and quality of care rendered once diagnosis is made. There is no known clinical study of a group of patients in which adequate supportive treatment alone has been compared with a carefully matched group of patients who received adequate supportive treatment plus some standard form of analeptic therapy. The studies that have been made always involve comparison of groups treated in one location with groups treated with other methods in different locations and with different personnel.

Experimental studies in animals also give no adequate basis for a definite decision. Numerous experiments utilizing a wide variety of animal species show that picrotoxin does decrease mortality from barbiturates. However, in such experiments no supportive treatment is given to the animals, so that they are not applicable to the clinical situation. There are no known experiments in which animals poisoned with barbiturates were given intensive supportive treatment and comparisons made between groups that received analeptics and groups that did not receive analeptics. Properly controlled experiments of this sort would do a great deal to clear up the problem.

This consultant has abandoned the use of analeptics in acute barbiturate poisoning. Reasons for so doing include those given below: 1. There is a lack of convincing evidence that analeptics lower the mortality rate in human poisoning. 2. Effects of analeptics, even those of picrotoxin, are very transient in patients poisoned with barbiturates. 3. There is danger of an

overdose of analeptics, with resultant necessity of giving more barbiturates to control convulsions. 4. Use of analeptics tends to reduce the quality of the supportive treatment. 5. This consultant has had no fatalities from bariturate poisoning since abandoning the use of analeptics more than five years ago.

All observers agree that intensive supportive treatment should be given, regardless of whether analeptics are used, and also that, when analeptic treatment is used, it should be reserved for cases of moderately severe and severe poisoning and should not be used in cases of mild poisoning. Recently it has been shown that repetitive electrostimulation increases depth of respiration in barbiturate poisoning. It was originally thought that such electrostimulation had to be applied to the head, on the theory that direct stimulation to the brain was necessary to induce respiratory stimulation. It is now known that the application of electrical current to any part of the body has the same effect and is abolished by anesthetizing the area under the electrodes with procaine. Respiratory stimulation resulting from electrostimulation, therefore, is reflex in origin and does not differ from respiratory stimulation resulting from the application of a variety of painful stimuli. It is, however, a good method of obtaining respiratory stimulation in a controlled way and, therefore, may have a limited place in the treatment of barbiturate poisoning. Daptazole and Megimide are available for investigational use only. Information can be obtained by writing A. & G. Nicholas, Ltd., c/o Muller & Phipps (Asia) Ltd., 1 Park Ave., New York.

PREGNANCY ASSOCIATED WITH CIRRHOSIS

To the Editor:—*A 39-year-old woman under routine care for alcoholic cirrhosis of the liver has become pregnant. Is there any constant effect of one condition on the other?* *M.D., Iowa.*

Answer.—According to Burslem, Gardikas, and Israels (*J. Obst. & Gynaec. Brit. Emp.* 59:777, 1952) only 10 cases of pregnancy associated with cirrhosis of the liver have been reported. They add two cases. There are many reasons for the extreme rarity. Most females with cirrhosis of the liver are in the age beyond childbearing. The metabolism of the sex steroids is disturbed in the presence of failure of the liver parenchyma, and hence fertility may be impaired even in early cases of cirrhosis. Pregnant women who have cirrhosis of the liver should have a diet high in protein and rich in calories. The first patient reported by Burslem and associates had marked hepatosplenomegaly and impaired liver-function tests, but she went successfully through her pregnancy and puerperium. The second patient, in whom the diagnosis was confirmed by laparotomy, went successfully through two pregnancies. There was no evidence that pregnancy had any injurious effect on the health of these mothers. The prognosis of pregnancy in a patient with hepatic cirrhosis does not seem to be universally unfavorable. Regular medical and obstetric follow-up and close collaboration between internist and obstetrician are essential for the successful management of a case of pregnancy complicated by cirrhosis of the liver.

SERUM SICKNESS TYPE OF REACTION

To the Editor:—*A man who sustained a puncture wound by striking a rusty nail had never received tetanus antitoxin or toxoid but had no prior allergic reactions. An intradermal test with tetanus antitoxin was done, and 300,000 units of penicillin were given intragluteally. After one-half hour, there was only a minimal wheal in the skin of the forearm, with no surrounding erythema or local itching; 1,500 units of the tetanus antitoxin was injected intragluteally, and Pyribenzamine was given. Seven days after the injection of serum and penicillin he returned with a generalized urticarial rash of trunk and limbs. The hives disappeared after injection of Benadryl. Pyribenzamine tablets were dispensed, and four hours later the patient reported he felt nauseated but that 99% of the itching had been relieved. Two days later it was learned that he had been hospitalized "with a severe reaction and paralysis." The latter proved to be immobilization from multiple joint pain and cleared a few days after administration of antihistamines and intravenous injection of calcium gluconate. A few weeks subsequently the patient again required hospitalization for recurrent skin and joint symptoms, at which time prompt relief followed treatment with corticotropin. It has been two months since the initial treatment, and there is again present an acute outbreak of generalized hives, accompanied by swelling of the joints and ankles and knees. Have you any suggestions for further treatment? Does serum neuritis with palsy ever develop as late as two months after the injection of tetanus antitoxin? Would the symptoms described suggest possibly a penicillin reaction? How soon would it be advisable to consider beginning the active immunization of this individual by the subcutaneous injection of tetanus toxoid?* *M.D., California.*

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—The "serum sickness" type of reaction described here could be caused by either or both the antitoxin and penicillin injections. The delay of seven days (usually longer) before the onset of symptoms indicates that allergy developed to one or to both of the substances during the interval. Recurrent or persistent symptoms of urticaria and joint involvement may last for many months as a result of either penicillin or horse serum sensitivity, even as long as nine months. In the absence of the usual contraindications to their use, corticoids or corticotropin may be given if antihistamines alone fail to control further acute attacks. These hormones are especially useful in the self-limited type of reactions characteristic of drug allergy. There is no reason for delaying immunization of this patient with tetanus toxoid. In the future he should receive penicillin or horse-serum-derived antitoxins only after careful consideration of possible sensitivity to either of these. The frequency with which penicillin is used makes it the more dangerous of the two. It would be preferable to use other antibiotics than penicillin in this patient. If the use of penicillin is considered important for any future infection, skin

tests by scratch followed, if necessary, by intradermal testing should first be done to determine the absence of sensitivity before it is administered. Severe and even fatal anaphylactic reactions may occur in such patients as the one described here if sensitivity has been acquired to penicillin or horse serum. For scratch test, the undiluted drug may be used. For intradermal test, a solution of penicillin G (1,000 to 5,000 units per milliliter) is usually used. It should be noted first that the intradermal test with penicillin may be dangerous in highly sensitive patients and that a negative skin test may sometimes occur despite the presence of clinical sensitivity to the drug. In view of the history presented, a positive skin test to either penicillin or horse serum should warn of the likelihood of a severe reaction if administered.

ANSWER.—A patient with a wound of the type described should receive prophylaxis against tetanus. For patients not previously immunized by a series of two or three tetanus toxoid injections, passive immunization with 1,500 units or more of tetanus antitoxin given intramuscularly is indicated. For individuals seen more than 24 hours after injury, the dose of antitoxin may be doubled for each day of the lapsed time up to a total of 12,000 units. Since this patient had received no previous active immunization, passive immunity in the form of administration of tetanus antitoxin was indicated. From the symptoms and the course reported, it would appear that this patient developed serum sickness from the tetanus antitoxin with generalized urticarial reaction and arthritis. Serum neuritis has been reported to develop slowly, and the motor impairment may become detectable as late as three months after the administration of the serum. Active immunization of this individual by the injection of two or three doses of 0.5 to 1.0 cc. of alum-precipitated toxoid at intervals of three to four weeks may be instituted at any time for the purpose of active immunization. Active immunization against tetanus could have been started concurrently with the administration of the tetanus antitoxin providing the toxoid had been injected with a separate syringe and needle into a different part of the body than was the antiserum.

DOSAGE OF VITAMIN B_{12}

TO THE EDITOR:—*I have been informed that massive doses of vitamin B_{12}, such as 1,000 mcg., are no more effective than doses of 100 mcg. I would appreciate an opinion in this matter.*

Bert P. Austin, M.D., Utica, N. Y.

ANSWER.—Presumably this inquiry relates to the parenteral route of administration. Intramuscularly given doses of 1,000 mcg. (1 mg.) of cyanocobalamin are far in excess of those required in the proper treatment of pernicious anemia. Suitable dosage schedules for the use of this vitamin may be found in New and Nonofficial Remedies, in standard textbooks of therapeutics, and in numerous reports published during recent years, including the recent article, "Folic Acid and Vitamin B_{12} in Medical Practice," prepared for the Council on Foods and Nutrition of the American Medical Association by Walter G. Unglaub and Grace A. Goldsmith (*J. A. M. A.* **161**:623 [June 16] 1956). These authors state: "The amount of vitamin B_{12} required for maintenance therapy of patients with pernicious anemia is approximately 1 to 2 mcg. daily. The giving of 100 mcg. intramuscularly at monthly intervals has been found satisfactory for most patients. The use of larger doses given at longer intervals does not seem advisable since the amount of vitamin excreted in the urine increases as the dosage is raised."

Others have called attention to the fact that doses of cyanocobalamin higher than 100 mcg. are generally unnecessary because most of a single massive dose is rapidly excreted in the urine. Although preparations containing 1 mg. or more of cyanocobalamin per cubic centimeter have been employed on an experimental basis in various diseases unrelated to the anemias, the value of such therapy has not yet been adequately established. Regarding oral therapy of pernicious anemia utilizing high (milligram rather than microgram) doses of cyanocobalamin, Unglaub and Goldsmith state: "Such therapy is not recommended for routine use at the present time, but it offers some advantages in respect to the flexibility of treatment and the standardization of oral dosage, which merit further study."

UNEXPLAINED ITCHING OF 25 YEARS' DURATION

TO THE EDITOR:—*A 65-year-old Chinese man has a 25-year history of intolerable itching of the face. At the beginning, the itching was limited to the central portion of the face, but for the last six months it has involved the entire face, scalp, neck, axillas, and groins. The first 20 years it occurred only in the late afternoon or when there was a temperature change during the day. At present, it occurs on the slightest provocation, such as a touch, sweat, increased humidity, occasionally some foods, and alcoholic beverages. Very often, however, it starts without any obvious reason. Vigorous scratching gives relief for only a few hours. The condition is considerably improved during cold weather and when he has a high fever or is hungry, and it disappeared for two weeks when he had a heart attack two years ago. Physical and laboratory examinations are negative, except for the hypertension for the past 10 years (170/90 mm. Hg). He has been treated with different "cooling" lotions, blue light, x-ray, vaccination, and various diets, with only temporary relief. What type of approach could be used in determining the cause of the itching?*

M.D., Rhode Island.

This inquiry was referred to two consultants, whose respective replies follow.—ED.

ANSWER.—Presumably, in this patient there is itching without dermatitis or cutaneous change of any kind. One must therefore rule out causes of itching such as systemic diseases, especially endocrine, nephritic, and hepatic disorders. The 25-year duration would seem to eliminate visceral malignancy or lymphoblastic diseases. Toxic-allergic reactions to food or drugs, especially narcotics, must be considered, as must psychogenic and environmental factors, for he had no trouble when he was removed from his environment by his heart attack. The cause might well be in one of the last-named factors, and these should be explored.

ANSWER.—There are two important items missing from the question. Such unexplained itching could be due to allergy, and there should be mention of whether the patient has had hay fever or asthma in the past or has them now. The second missing item concerns the physical examination. It is "negative," but if so, it is surprising that "intolerable itching" relieved by scratching should not produce some change in the skin. If further study of this patient's history reveals evidence of allergy, it is possible that changes in the itching can be related to changes in season, environment, or diet, and so give a clue to the cause of trouble. If, however, both signs and symptoms include nothing except itching and hypertension, and if the symptom has continued for 25 years, then one must think of a psychogenic cause. Questions about his mode of life, his family, his work, and any problems in his life might be revealing. One must be sure about drugs, for the long-continued use of a vegetable cathartic, a barbiturate, a vitamin, or even saccharine for sweetening could produce this picture. Finally, leukemia, scleroderma, lupus erythematosis, and Hodgkin's disease can all cause such chronic pruritus, but these diseases could hardly be expected to last for 25 years without there being physical evidence of their presence. Cortisone and corticotropin (ACTH) might be considered later, but not until all studies have been made and all other treatments tried first.

INGESTION OF BROKEN GLASS

TO THE EDITOR:—*If a person accidentally swallows broken glass, what kind of treatment is advisable?*

M.D., New Jersey.

ANSWER.—Regarding the effects of the swallowing of glass, Simmons and Glahn (*J. A. M. A.* 71:2127 [Dec. 28] 1918) stated that they had not obtained positive data concerning a single authentic case of illness due to its ingestion in any form or size. After feeding ground glass and various-sized particles of glass to dogs they reported that the ingestion of glass has no toxic effect and produces no lesions either gross or microscopic on the gastrointestinal tract of dogs. The observations that have been made on glass eaters have also caused some medicolegal authorities to question the dangerous properties of pounded glass. However, cases of mediastinitis and peritonitis have been observed following the perforation of the alimentary tract. Rectal abscesses also may occur. A person who has swallowed glass should be examined roentgenologically to locate, if possible, any opaque glass. The esophagus should be explored by laryngoscopic and esophagoscopic examination. If the patient is seen soon after ingestion of the glass, an effort might be made to evacuate the stomach. It is usually difficult to do this with a stomach tube or pump because of the clogging of the tube by the glass particles. Large quantities of a mucilaginous substance such as gastric mucin or Metamucil or Mucara may be given, and then vomiting may be induced by apomorphine or by tickling the fauces. There is some risk that in the act of vomiting particles of glass may cut the stomach or esophagus. After evacuation of the stomach, a large amount of mucilaginous or soft bulky indigestible material should be given to form a soft envelope for any glass particles remaining in the alimentary tract. Opiates should not be given for pain because of the danger of sphincter spasm producing cutting of the walls of the alimentary tract. If there is no bowel movement, an enema of a mucilaginous or oily material can be given, since in some cases the glass successfully traverses the entire alimentary tract only to lodge at the rectal sphincter. Daily rectal digital examination should be performed. If symptoms of mediastinitis or perforation of the stomach or intestine occur, antibiotics should be given, followed by prompt surgical intervention.

TICK BITES

TO THE EDITOR:—*A 30-year-old man is subject to wood tick bites when hunting and fishing. On removal of the tick, the usual erythematous papule, which is intensely pruritic, subsides in a matter of days, leaving a macular, slightly brown discolored area at the site of the bite. These areas are then subject to a recurrence of the primary skin reaction, in which they become red papules, intensely pruritic and distracting to the patient. A careful history does not reveal a new contact with wood ticks, which fact would make the above-described circumstances bona fide recurrences. Can you offer suggestions as to the pathology of these lesions and as to their treatment in the recurrent phase?*

Donald E. Kuenzi, M.D., Gashland, Mo.

ANSWER.—It is assumed the trouble from tick bites is due to the Lone Star tick, Amblyomma americanum. This tick is rather abundant in the Ozarks and attacks man freely in each of its active stages: larva, nymph and adult. This tick has a rather long, toothed hypostome or beak that is frequently broken off in the skin when the tick is removed. The presence of the hypostome in the skin usually intensifies and prolongs the pruritus. After a tick inserts its beak, a salivary secretion is introduced, which retards coagulation and produces irritation, bringing an increased blood flow to the point of attachment. The amount and persistence of inflammation and pruritus produced by a tick bite varies widely in different individuals. The persistence of pruritus also varies much, however, many individuals suffer recurrent pruritus that may last a year or more. No thorough study has been made of the pathology of these lesions, nor has any highly effective treatment been developed. Cooling ointments, such as menthol, have given some relief; carbolated (2%) petrolatum is also helpful.

Avoidance, as far as possible, of tick bites is important both from the standpoint of unpleasant local effects and because of the hazards from Rocky Mountain spotted fever and other rickettsial diseases, tularemia and relapsing fever. This is not easy. Protective clothing is important. This consists of closely woven smooth trousers with high-top shoes laced over the bottom of the trousers. It is helpful to watch for adult ticks or clusters of young ticks crawling up the clothing and to brush them off.

No chemical has been found that is 100% perfect as a repellent against ticks. Spraying the shoes and clothing with the repellent developed by the Orlando, Fla.,

laboratory of the U. S. Department of Agriculture, known as 6-2-2, gives much protection. This material, consisting of six parts dimethylphthalate, two parts Indalone, and two parts Rutgers 612, is now commercially available. Ticks that succeed in attaching should be removed as soon as possible to avoid infection with rickettsial diseases and to reduce inflammation. Remove ticks with a steady pull. If the beak is broken off in the skin remove it surgically. Apply tincture of iodine to the bite. If a tick is very difficult to remove, apply carbolated petrolatum to it and, if it does not let go in an hour, pull it out.

SUDDEN DEATH AND CLIMATIC CHANGE

To the Editor:—*A 35-year-old patient spent 13 months in Greenland and then went to the midwest, where for the 4½ months before his death he endured unusually hot and humid weather. Although his health had apparently been good, at 4 a. m. one day he suddenly had a convulsion, became cyanotic, frothed at the mouth, and was incontinent of urine. Within 5 to 10 minutes he died. An autopsy was performed that same morning, but the pathologist could find no cause of death. Microscopic examination after autopsy revealed passive congestion of the lungs, spleen, kidney, and liver and marked toxic degeneration of the kidneys. Toxicologic examination of stomach contents was entirely negative for a wide variety of poisons and drugs. Is there any possibility that the marked climate change had anything to do with his death?*

William H. Davis, M.D., Sherman Oaks, Calif.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—The query does not allow of any definite answer as to the cause of death. The pathological concomitants enumerated could be due to a variety of causes, such as poisons, viral infections, and pyrogenic toxins. A pathologist who has had considerable experience in the pathology arising from the high temperatures found in desert regions could give no explanation for the death described.

Answer.—It is impossible to be sure of the cause of death in this case. The findings described would be compatible with heat prostration. It is unusual to have death from this cause occur at 4 a. m. when presumably the patient had no untoward symptoms when he went to bed. Transfer from an extremely cold to an extremely hot and humid locality could unquestionably have been a factor in the heat prostration, although as a rule acclimatization should have occurred within four and a half months. No mention is made of whether he had been in an airplane. If he had been chilled and subjected to low oxygen tension due to high altitude the afternoon before death, presumably the intense heat on the ground would have been an even more important environmental insult. Possibilities other than heat stroke here are epilepsy, hyperinsulinism, and adrenal insufficiency. The questioner would probably find Bean's chapter on Physical and Toxic Agents in Sodeman's "Pathologic Physiology" of considerable interest.

PSEUDOACUTE ABDOMEN IN DIABETIC WOMAN

To the Editor:—*A diabetic woman aged 48, was found to have an acute abdomen of sudden onset. She had severe colicky pains in the right lower quadrant, distention, moderate shock, and no vomiting. Decubitus films showed a huge distended intestine, which the radiologist called small intestine and which showed marked fluid levels. The abdomen sounds were absent, although the internist said he could pick up a very small tinkle. There was some tenderness and rigidity in the right lower quadrant, but it was not marked. No masses could be palpated. Conservative treatment after about six hours did not reveal any improvement. Laboratory studies showed blood sugar level, 333 mg. per 100 cc.; blood amylase, 4 units per 100 cc.; and glycosuria, 4+ with a trace of acetone. The patient stated she had had a similar but milder spell several years ago. At operation she had a volvulus of the splenic flexure region of the colon, with beginning gangrenous changes. However, the intestine was still viable, and pulsation was felt in the arteries distal to the twist after it had been reduced. She had a very redundant colon. Another significant finding was that there was practically no pancreas. The questions are (1) what is the mechanism of this pseudoacute abdomen in diabetics other than the one mentioned above, (2) is a redundancy of the colon a significant finding in chronic diabetes, and (3) is the increase in the size of the colon in some way related to the atrophy of the pancreas on a physiological basis?*

S. W. Scorse, M.D., Joplin, Mo.

Answer.—A pseudoacute abdomen is uncommon in diabetics who do not have acidosis, but it is often encountered when diabetics are in the early stages of diabetic coma. It may require three or four hours to determine whether organic disease is present, thus leukocytosis may occur in both conditions; fever may be absent in appendicitis. Unfortunately, only too often in diabetics are the symptoms of appendicitis masked and, unless the closest attention is given, appendicitis may go on to perforation of the appendix when the patient is under treatment for some complication or enters merely for indigestion. The treatment of the case just cited is more than commendable, but, since a volvulus was found, the condition of the abdomen could hardly be said to be pseudoacute. On inquiry of surgeons who have had unusual experience with diabetics, they confirm my opinion that a redundance of the colon in diabetics is no more frequent than in a similar group of persons with surplus weight who do not have diabetes. My colleagues in pathology do not think that an increase in the size of the colon is related in any way to an atrophy of the pancreas, save that anomalies are much more frequent in diabetics than in persons who do not have diabetes, as shown in studies of diabetic children. Diabetic neuropathy, when the visceral autonomic system is involved, may cause severe abdominal pain, obstipation, and dilated atonic intestinal loops.

AZOOSPERMIA AND VARICOCELE

To the Editor:—*A patient desirous of having children was found to have azoospermia on one examination. He also has a varicocele on the left. A recent article stated that after operation for removal of varicocele about 50% of these persons were able to have children. Please comment on this point and on any other type of treatment.*

H. E. Woodbury, M.D., Akron, Ohio.

Answer.—The presence of a varicocele has no direct bearing on the problem of sterility. A varicocele of moderate size causes no significant alteration of the circulation of the testis and does not have any direct effect on spermatogenesis. Surgery for the varicocele is certainly not indicated as the treatment for sterility, nor would it be expected to have any effect. If this patient has a complete azoospermia on one examination, he should have at least one or two other specimens of semen examined to be sure that this is a consistent finding. If complete absence of spermatozoa is found in all specimens, then the indications are for a testicular biopsy to determine whether there is spermatogenesis within the testis itself. If there is, one should look for a block in the spermatic ducts, through either the epididymis or the vas deferens. If the defect is in the spermatogonia themselves, treatment is of very questionable value.

LOSS OF MEMORY AFTER ELECTROSHOCK THERAPY

To the Editor:—*A 67-year-old woman received, within seven weeks, 20 electroshock treatments for acute depression, anxiety, and agitation. In addition she received large doses of sedatives and tranquilizers. Her previous complaints more or less improved, but symptoms developed during and after the treatments that were not present before. One of these is a partial "swiss-cheese-like" loss of memory that is very embarrassing, as it occurs with names of close friends and with events and facts that were very familiar with her. Will this loss of memory be permanent, or will it improve as time goes on? Is there anything that can be done to hasten recovery?*

Arthur H. Steinhardt, M.D., Springfield, Mass.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—Disturbance of awareness of memory contents is a rather characteristic side-effect of electroshock therapy, especially when a large series of treatments at relatively high amperage of current is necessary to bring about recovery from agitated depressions. These memory defects usually clear up within three to six months. With sympathetic guidance and skillful psychotherapy, and especially with encouraging explanation, this trying period of gradual return of awareness of memory contents can be rendered less harassing to the patient. It is important to give such help to the convalescing patient, since excessive concern over this defect may sometimes trigger relapse. Sometimes this experience of reduced awareness for memory contents may become neurotically fixed, a complication that the psychiatrist can diagnose and help the patient through by aiding him in reality testing. Such help enables the patient to realize that the memory disturbance no longer exists. A patient claimed that even a simple thing like finding the way to her son's house had been so completely and irretrievably forgotten that she could not drive or walk there. Her husband was advised to deliberately take a wrong turn on one of their trips to the son's house, and the patient immediately called her husband's attention to the presumed error. This was utilized to point out the fact that her memory had actually returned. This occurred three months after the last electroshock treatment; concern with her memory vanished from then on, and the patient achieved complete recovery. When the patient's memory disturbance lasts longer, nonconvulsive electric stimulation may sometimes relieve it (see Alexander, L.: Treatment of Mental Disorder, Philadelphia, W. B. Saunders Company, 1953). This was confirmed by a number of careful observers, most recently by Fabing (*J. Nerv. & Ment. Dis.* **121**:19, 1955).

Answer.—The question describes a not uncommon undesirable effect following on a course of electroshock therapy. An important detail that would be needed to discuss the problem adequately is the date of the last electroshock treatment. Assuming it was recent, the course described is reasonably typical when one considers the concentration of therapy and the patient's age. It should be said that this patient of 67 years received many treatments in a short period of time; therefore, the relatively profound mental defect is not particularly unusual. However, it is more profound than one would expect in a younger person. The loss of memory is not permanent, and further improvement may be expected. Recovery of memory is usually complete except for little islands of events that happened immediately before and after the course of electroshock, an amnesia of sorts. These islands of permanent forgetfulness are minimal and as a rule are not great enough to interfere with the patient's enjoyment of living. If these symptoms persist unduly, then it may be that depression is clouding the field; it would take a rather thoughtful psychiatric evaluation to determine this point. Nothing can be done to hasten the disappearance of these symptoms besides a supporting therapeutic relationship that deals effectively with the patient's symptoms. Reassurance is in order. A thorough evaluation of her trouble by a psychiatrist, perhaps with the aid of certain psychological tests, would be useful as a therapeutic maneuver in the event the syndrome continues.

ALOPECIA CICATRISATA

To the Editor:—*Is there any recent information on the cause and the treatment of alopecia cicatrisata (pseudopelade)?*

G. J. Maloof, M.D., Madison, Wis.

Answer.—The cause of alopecia cicatrisata is unknown. There is no recognized treatment for this condition. However, it may be difficult or impossible to differentiate this entity from discoid lupus erythematosus. Under these circumstances, it would be permis-

sible to attempt treatment with an antimalarial agent such as chloroquine, 250 mg. by mouth four times a day. Associated complaints should receive indicated care.

USE OF CORTICOTROPIN WITH PREDNISONE

To the Editor:—*A 30-year-old woman with acute disseminated lupus erythematosus has had excellent control of her disease with administration of 15 mg. of prednisone daily during the past nine months. Is it desirable to withdraw this medicament for a brief period and substitute corticotropin (ACTH) to prevent adrenal atrophy? If so, please outline an acceptable regimen that will accomplish this purpose.*

L. David Comstock Jr., M.D., Dowagiac, Mich.

Answer.—This patient should receive whatever amount of corticosteroid therapy is necessary to keep the symptoms under control. It would be well, if possible, to reduce the dosage gradually rather than to withdraw the prednisone abruptly; if a daily dosage of more than 5 mg. must be employed, it would be well to substitute corticotropin one day each two weeks.

PATHOLOGY OF MYOCARDIAL INFARCT

To the Editor:—*What could be the pathological basis of a myocardial infarct in a man in his fifth decade with no discernible arteriosclerosis (eyegrounds and peripheral), with a family history of longevity, with systolic blood pressure readings averaging 90 to 100 mm. Hg, and with dietary habits naturally tending to restriction of fats (although his cholesterol level is elevated)? Is the hypotension itself, if of long standing, a possible factor?* *M.D., Pennsylvania.*

Answer.—The pathological basis of a myocardial infarct in such a man could be any one of many etiological factors that might be difficult to ascertain or evaluate at this time. It is not known what previous infectious conditions such as typhoid, tonsillitis, or scarlet fever or what metabolic conditions such as hypothyroidism or diabetes do to the arterial bed. It is not known if an abnormal vascular tree was present in the heart. It is known that different groups of individuals have a proneness to arteriosclerosis of the coronary vessels, the renal vessels, or the peripheral vessels of the legs. No reason is known for the selection of these sites in different individuals. In the light of our present thinking, high blood cholesterol levels may be a mere accelerating factor in producing a myocardial infarct. Many combinations of these several variables could be the reason for this patient's attack. It is doubtful that a history of familial longevity will necessarily always mean that offspring will have long lives. Disease can always alter such family endowments. It has actually been established by historical studies that coronary disease often occurs at progressively earlier ages in succeeding generations of persons with the disease.

ANOGENITAL RASH IN A DIABETIC

To the Editor:—*What could be suggested for controlling a rash involving the anogenital region in a 2-year-old diabetic?*

Anthony J. Bamonte, M.D., Philadelphia.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—The treatment depends on the diagnosis and the severity of the eruption. If it is a simple diaper rash, the application of a soothing paste such as equal parts of Lassars Paste and petrolatum may suffice. If moniliasis is present, it might be well to apply Mycostatin in a drying-type lotion.

Answer.—Such rashes may be due to glycosuria and associated yeast infections of the perigenital and perianal regions. Probably the best method of control is reduction of glycosuria to the lowest possible level compatible with safe control and the use of one of the yeast-inhibiting drugs on the market.

TACHYCARDIA

To the Editor:—*In the Queries and Minor Notes section of* The Journal, *Dec. 1, 1956, page 1351, a question is asked about a patient with postprandial tachycardia and distress. The increase in myocardial irritability following meals is sometimes related to postprandial (relative) hypokalemia. The same mechanism plays a role in the "meal test"—a tracing taken after a high-calorie meal compared to a fasting record. This is sometimes useful in the diagnosis of arteriosclerotic heart disease in patients with normal electrocardiograms; a positive test shows ST and T wave changes, premature beats, and arrhythmias. In such cases, 1 or 2 Gm. of potassium chloride taken with meals may modify the electrocardiographic changes and relieve the symptoms.*

Thomas T. Tamlyn, M.D.
115 E. 72nd St.
New York 21.

The above letter was referred to the consultant who prepared the answer to this query, and his comments follow.—Ed.

To the Editor:—*It would be difficult to evaluate the role of potassium in the postprandial tachycardia, dyspnea, and arm pain in the 75-year-old woman. The concentration of potassium in the extracellular fluid has a profound influence on cardiac muscle irritability, probably mediated through enzyme systems located in the cell membrane. There is poor correlation, however, between the serum potassium level and the electrocardiographic tracing. The electrocardiographic changes described after a high-calorie meal are similar to those seen after exercise in some patients with arteriosclerotic heart disease with angina. It is felt that these electrocardiographic changes are caused by transient subendocardial ischemia precipitated by the exercise. There is no objection to a trial course of potassium chloride, provided that renal function is adequate.*